

Frontispiece Photograph of the face from the first known North American case of coccidioidomycosis (From Rixford and Gilchrist *Johns Hopkins Hospital Reports* 1 209 265 1896 )

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# COCCIDIOIDOMYCOSIS

*Foreword by*

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TO JANETTE

# Foreword

FROM THE time of Posadas Rixford and Ophuls at the end of the century till Gifford and Dickson s break through" of Valley Fever in 1936 knowledge of coccidioidal infections proceeded at a leisurely and orderly pace However in the past twenty years progress has been constantly accelerating A monograph on coccidioidomycosis is very timely Beck s Bulletin 57 of the California State Department of Public Health summarized most of our knowledge of the earlier era but even it was incomplete With so many new workers attracted to this subject a monograph summarizing past studies is invaluable To be of maximal worth such a monograph must provide a perspective of the total field

We are very fortunate that Marshall Fiese recognized this need and has met it admirably With his undergraduate and graduate medical training in the classrooms laboratories and wards where Rixford Ophuls and Dickson taught and studied Dr Fiese was steeped in this subject I recall Dr Fiese then our outstanding Resident in Medicine telling me after we had seen a patient with disseminated coccidioidomycosis on the Men s Medical Ward that he planned to practice in the San Joaquin Valley Later I learned that he had accepted a position in the Fresno Veterans Administration Hospital I congratulated him and emphasized the superb opportunity he would have for coccidioidal studies in keeping with his lineage Indeed Dr Fiese is fulfilling superbly the responsibilities of this charge Through the years he has been a diligent student and has published excellent original research Equally importantly he has seen and treated all the varieties of the coccidioidal diseases viewed countless roentgenograms seen and studied the tragic autopsies and perhaps most importantly of all lived for years in the coccidioidal countryside This is the environment in which he has read and studied the many hundreds of papers on coccidioidomycosis As this monograph reveals Dr Fiese has been living this subject Coccidioidomycosis has been figuratively and literally a member of my own family As Marshall Fiese describes it I see it vividly accurately and deftly revealed Indeed its portrayal is in more intimate detail than anyone else ever has grasped It is authoritative without being authoritarian In its friendly tone one of his monograph s greatest contributions should be that of infecting many others with a fascination for this subject a form of intellectual mycosis One hopes that it will also liquidate some of the harrassing and detrimental hypotheses

with which some of the inexperienced and unsophisticated have been gulled The monograph should be a major factor in making succeeding decades even more productive than the last two

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# Preface

When I was a medical student at the Stanford University School of Medicine I was often intrigued by a striking picture—part of an old medical convention exhibit which had been set aside in one of the hallways It was a greatly enlarged photograph showing the face of a poorly dressed farmer with an unusual skin lesion that made him look pathetic and ugly I wondered who he was and why his likeness had been put in the display

One day long afterwards while reading the 1896 paper of Rixford and Gilchrist—the first North American description of coccidioidal disease—I found the same photograph and read the story behind it It was the face of poor Joas Furtado Silverra (Frontispiece) the first patient with coccidioidal granuloma to be followed to the end and the first of thousands of Californians known to have suffered the ravages of fungus *Coccidioides*

This book is the story of *Coccidioides immitis* and the varied disease it causes Although coccidioidomycosis is no longer a rare and exotic affliction knowledge about it is not so old but that it still has an air of mystery both to layman and physician In popular magazines the account of its denouement is compared to the thrilling story of Walter Reed and Yellow Fever Except in highly endemic areas the discovery of a new case is still the subject of a medical paper Nevertheless in the past fifty years knowledge about coccidioidomycosis has become as precise as that about any other serious mycotic infection *Coccidioides* has become a type fungus for mycologic investigation Yet there is no source where one can find concentrated within the pages of one book the growing mass of information about it There have been many excellent reviews of the subject notably those by Dr Charles E Smith but one must hunt through the periodic literature for them This book has been written in an attempt to bring together in one place the historical mycological pathological and clinical aspects of coccidioidal disease

Although I am a native of the San Joaquin Valley of California it was as a medical student at Stanford that I first heard of "San Joaquin Valley Fever Those were the days not long after the renaissance in the study of coccidioidal infection when knowledge was young and its growth was exciting With more enthusiasm than judgment we put coccidioidomycosis" into nearly every differential diagnosis We could usually depend on having a histologic slide of coccidioidal granuloma as an unknown" in examinations in Pathology Once when I could find nothing diagnostic on a slide except a few inflammatory cells I decided that in the absence

of everything else, there must be some spherules somewhere—so I diagnosed coccidioidal granuloma and passed handily

The contagious enthusiasm of Dr Charles E Smith, who was then at Stanford was in large part the reason for my early interest in coccidioidal disease The resulting friendship has matured since I have returned to my native San Joaquin Valley and has been the stimulus necessary to the assembling of the data contained in this book

My obligations are more than I can number to my medical confreres in the San Joaquin Valley, who with a hint here and there opened up new avenues of thinking to the staff of the Fresno Veterans Administration Hospital (Dr Forrest G Bell Manager Dr Stephen Chen Chief Medical Service, Mr Royal Sorensen bacteriologist and many others) to Dr Gordon A Diddy and his staff at the General Hospital of Fresno County to my secretaries, Mrs Harry G Sidorin and Miss Doris Bowen and my mother, Mrs Jesse T Fiese, who patiently copied and re copied the manuscript, to Miss Mary Hess librarian at the Fresno Veterans Administration Hospital and Mrs Marghuretta Golden and Mrs Lucille Buccieri librarians at the General Hospital of Fresno County, and most of all to the scores of physicians and scientists of North Central and South America who so kindly shared with me their photographs their wisdom and their devotion to mankind

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# COCCIDIOIDOMYCOSIS

*Chapter One*

# The Present Importance of Coccidioidomycosis

Importance in Endemic Areas
Importance in Non Endemic Areas

## IMPORTANCE OF COCCIDIOIDOMYCOSIS IN ENDEMIC AREAS

For the *first time in the world s long history coccidioidomycosis is assuming* the proportions of an important disease Until the last two decades it has been but a rare and mysterious affliction as little relevant to American medicine in general as filariasis or kala azar Its present significance is in large part a by product of the westward migration of the American people In 1900 the population of the San Joaquin Valley of California was 108 000 In 1930 it was 440 000 At the present time it is well over a million and the monthly *increment is about 2 000 The population of near by Los* Angeles County increased 49 per cent between 1940 and 1950 During the same decade other southwestern states also saw a vast expansion varying from 20 per cent in Texas to 50 per cent in Arizona Nearly 700 000 acres of new San Joaquin Valley land most of it on the highly endemic west side have been put under cultivation since 1942 Many thousands of acres of the Sonoran desert in Arizona have likewise been turned into fertile farm land Each *year several million people travel in and through* the endemic areas of California and Arizona Two and a half million visit the National Forests and the National Parks—Yosemite Kings Canyon and Sequoia—at the eastern edge of the San Joaquin Valley In the decade between 1930 and 1940 many thousands of people migrated from the drought ridden states of the mid western dust bowl to the farm lands of central California Since World War II the influx from all the eastern states has continued *Hundreds of thousands of non immune people have*

thus come to share the San Joaquin Valley and the Sonoran desert with an ancient resident *Coccidioides immitis* the length of whose tenure here we have no way of knowing

The importance of coccidioidal disease does not lie in its frequency as a cause of death In the whole United States as C E Smith has pointed out there were only 353 deaths from coccidioidomycosis in the five years 1951 1955 less than half the number of fatalities which occurred on the highways during the single holiday weekend of Christmas 1956[illegible] The average number of deaths was only 71 per year Sixty per cent occurred in one state California

However when morbidity rather than mortality is considered the disease assumes a different importance In the most highly endemic areas—Bakersfield California Phoenix Arizona and El Paso Texas—nearly 100 per cent of the population will have been infected in a few years and about a fifth of them will have had an illness severe enough to cause temporary incapacity and to warrant medical care

Until July 1 1955 only disseminated coccidioidomycosis was reportable in California From 1893 when the first case was observed until the end of 1954 1 566 cases were reported or an average of about 25 new cases per year for the whole period During the first half of the entire span that coccidioidal disease has been recognized there were never more than twenty cases diagnosed per year and usually less than five With the rapidly increasing population since World War II the number has risen sharply so that since 1950 the average number of new cases per year has been nearly 75 (Table I) If dissemination occurs only once in 500 or so cases of primary infections there must now be about 35 thousand new infections yearly in California alone Since July 1 1955 active primary cavitary and disseminated coccidioidomycosis have all been reported together in one total figure but it is obvious that reports are being completed on only a tiny percentage of primary infections

All types of coccidioidal disease have been reportable in Arizona since 1942 There has been considerable variability in completeness of reporting as evidenced by the more than hundred fold variation in different years from a total of 5 in 1947 to 573 in 1956 (Table II) Ninety five per cent of the reported cases have been from the two counties of Maricopa (Phoenix Mesa and Chandler) and Pima (Tucson) counties in which are located the large military air fields (Table IV page 6) From the other 12 counties have come only 5 per cent of the reported cases As in California it is obvious that only a few of the cases of primary disease are actually being recorded The vigor with which reporting is done varies with local factors and personnel The number of deaths especially since 1950 has been much less variable and is probably a better index of a

TABLE I

INCIDENCE OF DISSEMINATED COCCIDIOIDOMYCOSIS IN CALIFORNIA 1903 1954

| *Year* | *Cases* | *Deaths* | *Year* | *Cases* | *Deaths* | *Year* | *Cases* | *Deaths* |
|---|---|---|---|---|---|---|---|---|
| 1893 | 1 | - | 1914 | 5 | 4 | 1935 | 28 | 14 |
| 1894 | 1 | 1 | 1915 | 2 | 1 | 1936 | 44 | 17 |
| 1895 | - | 1 | 1916 | 5 | 3 | 1937 | 38 | 27 |
| 1896 | - | - | 1917 | 4 | 3 | 1938 | 71 | 19 |
| 1897 | - | - | 1918 | 1 | 1 | 1939 | 73 | 21 |
| 1898 | - | - | 1919 | 11 | 4 | 1940 | 54 | 25 |
| 1899 | 2 | 1 | 1920 | 5 | 3 | 1941 | 41 | 17 |
| 1900 | 2 | 2 | 1921 | 8 | 7 | 1942 | 49 | 27 |
| 1901 | 3 | 1 | 1922 | 4 | 3 | 1943 | 31 | 23 |
| 1902 | - | 1 | 1923 | 16 | 4 | 1944 | 40 | 17 |
| 1903 | 1 | - | 1924 | 17 | 8 | 1945 | 43 | [illegible]1 |
| 1904 | 1 | - | 1925 | 8 | 4 | 1946 | 43 | [illegible]0 |
| 1905 | 2 | 1 | 1926 | 14 | 6 | 1947 | 63 | [illegible]0 |
| 1906 | 3 | [illegible] | 1927 | 19 | 7 | 1948 | 72 | 52 |
| 1907 | 3 | 1 | 1928 | 36 | 11 | 1949 | 91 | 60 |
| 1908 | 1 | - | 1929 | 46 | 25 | 1950 | 92 | 66 |
| 1909 | - | [illegible] | 1930 | 22 | 11 | 1951 | 64 | 43 |
| 1910 | 1 | 1 | 1931 | 19 | 8 | 1952 | 64 | 43 |
| 1911 | 4 | 1 | 1932 | 19 | 9 | 1953 | 91 | 56 |
| 1912 | 3 | 5 | 1933 | 54 | 25 | 1954 | 78 | 37 |
| *1913* | *4* | *3* | *1934* | *49* | *29* | | | |

Data for the years prior to 1928 when coccidioidal granuloma was first made reportable are from *Special Bulletin No 57 California State Department of Public Health* and the dates are those of diagnosis not of onset Data from 1942 onward include both civilian and military figures Compiled by Ida May Stevens Chief Morbidity Statistician California State Department of Public Health Courtesy of Dr C E Smith President California State Board of Public Health

TABLE II

REPORTED INCIDENCE OF COCCIDIOIDOMYCOSIS IN ARIZONA 1942 1956

| *Year* | *Cases* | *Deaths* |
|---|---|---|
| 1942 | 57 | 0 |
| 1943 | 222 | 0 |
| 1944 | 43 | 0 |
| 1945 | 7 | 1 |
| 1946 | 17 | 2 |
| 1947 | 5 | 6 |
| 1948 | 15 | 1 |
| 1949 | 89 | 2 |
| 1950 | 180 | 2 |
| 1951 | 180 | 7 |
| 1952 | 386 | 5 |
| 1953 | 97 | 8 |
| 1954 | 207 | 8 |
| 1955 | 164 | 7 |
| 1956 | 573 | 6 |

Compiled from data supplied through the courtesy of Clarence G Salsbury M D Commissioner Arizona State Department of Health

## TABLE III

### Origin of Reported Cases of Disseminated Coccidioidomycosis in California 1893 1954

| *San Joaquin Valley* | | *Sacramento Valley* | |
|---|---|---|---|
| Kern | 4/9 | Sacramento | 27 |
| Kings | 37 | Solano | 5 |
| Tulare | 99 | Yolo | 9 |
| Fresno | 122 | Placer | 1 |
| Madera | 17 | Colusa | 3 |
| Merced | 25 | Yuba | 1 |
| Stanislaus | 19 | Glenn | 2 |
| San Joaquin | 40 | Butte | 1 |
| | 833 | | 49 |
| | 55 0% | | 3 0% |
| *Southern California* | | *Other Counties* | |
| Santa Barbara | 9 | 11 coastal counties | 164 |
| Ventura | 14 | 7 mountain counties | 9 |
| Los Angeles | 299 | | |
| San Bernardino | 21 | Unallocated (transients) | 56 |
| Orange | 8 | | |
| Riverside | 16 | | |
| San Diego | 38 | | |
| Imperial | 3 | | |
| | 408 | | 229 |
| | 27 0% | | 15 0% |

* Adapted from *A Manual for the Control of Communicable Diseases in California* California State Department of Public Health 1956 p 59 By permission

## TABLE IV

### Origin of Reported Cases of Coccidioidomycosis in Arizona 191? 195?

| County | 1? | 43 | 4' | 4o | 4 | 47 | 48 | 49 | 0 | o1 | [illegible] | 3 | o' | o | [illegible] | Total | Per Cent of Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Apache | | | | | | | | | | | | | | 1 | 1 | | |
| Cochise | | 1 | | 2 | | | | 2 | 2 | 1 | 1 | | | | | 11 | |
| Coconino | | | | | | | | | | | | 1 | | 1 | | | |
| Gila | | | | | | | | | 2 | | 1 | 1 | 3 | 1 | 4 | 1 | |
| Graham | | | | | | | | 4 | 2 | 4 | 1 | 1 | | | | 1 | |
| Greenlee | | | | | | | | | | | | | 1 | | | 1 | |
| Maricopa | ∫ | 196 | 4 | 5 | 13 | 1 | 1 | 43 | ı3 | 64 | 134 | | 90 | 55 | 1 6 | 1 00[illegible] | 4 [illegible] |
| Mohave | | | | | | | | | | | | | | | | 0 | |
| Navajo | | | | | | | | | | | | | | 1 | | 1 | |
| Pima | | 4 | | | 4 | 4 | 14 | 3 | 58 | 10› | 4 | 31 | 106 | 9 | 385 | 11 3 | 50? |
| Pinal | 1 | | | | | | | | 10 | 4 | | 3 | 1 | 4 | | | |
| Santa Cruz | | | | | | | | | | | | | | 4 | 1 | | |
| Yavapai | | | | | | | | | | | | | | 1 | | 3 | |
| Yuma | | 1 | 1 | | | | | 3 | 3 | | | | 4 | 1 | | 7 | |
| State of Arizona | 5 | [illegible] | 43 | | 17 | 5 | 15 | 59 | 150 | 150 | 358 | 9 | 1 | 164 | 573 | [illegible]1 | |

Adapted from data supplied through the courtesy of Clarence [illegible] [illegible]bury M D Commissioner Ari[illegible] Department of Health

fairly constant rate of infection There must be five or ten thousand primary infections yearly in Arizona

The economic importance of coccidioidal disease in endemic areas can best be inferred from the accurately tabulated experience of military installations Hugenholtz[9,10] has reported that at Williams Air Force Base near Phoenix Arizona the man days of hospitalization for coccidioidomycosis greatly exceeded the combined total of man days of hospitalization for the three other most frequent acute illnesses (tonsillitis upper respiratory *infections and gastroenteritis) plus all traumatic injuries* The loss to the air field in working days alone was $35 000 Including the cost of hospitalization the expense was twice that figure Other Air Force Bases in the area have similarly estimated the total cost of coccidioidal infections at $50 000 to $100 000 yearly When the military experience is applied to the civilian populations of the whole endemic area the magnitude of the problem begins to be appreciated

The data from civilian hospitals are necessarily less precise because (1) a civilian hospital does not represent a community *in toto* as does a military hospital and (2) only a few of those stricken with coccidioidomycosis are actually hospitalized in civilian hospitals whereas in military service a man is either fit for duty or is under medical surveillance Nevertheless civilian experience bears out the conclusions mentioned above In a highly endemic area some physicians may see several fresh coccidioidal infections each week Nearly 400 patients were hospitalized for severe coccidioidomycosis at the Kern General Hospital Bakersfield California in the years 1951 1955 a quarter of them for disseminated disease many more were treated on an out patient basis In a similar period (1952 1956) 50 patients with definitely diagnosed severe coccidioidomycosis were hospitalized at the General Hospital of Fresno County California The average period of hospitalization was 31 days At $18 per day of hospitalization the cost to the county for each case was about $560 and for all of them about $28 000 These figures only begin to indicate the total cost of coccidioidal infections in the counties concerned for they do not include the cost of welfare aid to families of victims the economic *loss from inability to work and the expense incurred by the much larger* number of patients who were too ill to work but not sick enough to seek hospitalization

Another reflection of the economic importance of coccidioidal disease is the fact that insurance companies are becoming increasingly concerned about the problem of liability arising from industrial exposure to *Coccidioides* Because of the large numbers of non immune persons often of the susceptible dark skinned races who are attracted to agricultural work in the endemic areas underwriters are having to re evaluate the risk

involved in insuring employers of farm and rural labor Because insurance losses are categorized by occupation rather than by disease it is difficult to determine the total expense of compensating victims of occupationally incurred coccidioidal disease It is nevertheless well established that the loss has been considerable since the first recognition of coccidioidomycosis as an industrially incurred disease in 1930 There are cases on record in which compensation for total disability has been continuous for twenty years In view of the tendency toward increasingly liberal awards in all types of liability, the concern of the insurance underwriters is well founded

On the other hand it is as easy to overestimate the importance of coccidioidal disease as it is to belittle it Among the uninstructed—laymen and physicians alike—several legends have wide acceptance The first is that coccidioidal disease is so prevalent and so infectious that it is foolhardy to enter an endemic area Although infections do sometimes occur from fleeting exposure there are many long time residents of the San Joaquin Valley who have never clearly heard of the disease much less suffered because of it Another legend is that the infection is always devastating whereas in truth it is usually symptomless and only rarely serious Again the idea exists that if one gets the disease he must leave the endemic area forthwith in order to get well as if it were something like an allergy Actually of course once the organism is in the body the outcome has nothing to do with geography The patient either recovers and has a permanent immunity or—rarely indeed—suffers a serious complication no matter where he is If he leaves the endemic area another potential victim may come to take his place A further misconception causes all sorts of unrelated symptoms to be attributed to Coccidioides often by the layman himself but occasionally also by the physician Anxiety reactions neurasthenias and constitutional inadequacies have a ready explanation in "Valley Fever" The informed physician is often hard put to convince the patient that a vague indisposition of several years duration is not the "Valley Fever" for which he has been treated without benefit of laboratory studies or any other efforts at confirmation Other folk tales confuse coccidioidal disease with Western Equine Encephalomyelitis or tularemia (both also present in the San Joaquin Valley) and other entities—even "spring fever" Although the importance of coccidioidomycosis is real and considerable as much consternation is caused by irrational uninformed fear of it as by actual invasion by the fungus

## IMPORTANCE OF COCCIDIOIDOMYCOSIS TO NON ENDEMIC AREAS

Coccidioidomycosis is of importance not only to endemic areas but also to other parts of the world where it has been both a hazard and

indirectly a help In certain situations the danger of coccidioidal infection is actually greater outside of the regions of highest endemicity Laboratory infections for instance are more prone to occur where the fungus is not recognized as a constant danger and where due precautions are therefore not observed A number of infections some fatal have been contracted in laboratories far removed from the natural habitat of *Coccidioides immitis* The exact extent of fomite transmission of the disease is unknown The reported cases are few but since only chronic coccidioidal lesions would ordinarily be recognized in non endemic areas the number of cases of primary disease there is probably several hundred times as many

The disease is also of importance when patients return home from endemic areas Since World War II many chronic infections have been seen in clinics and Veterans Administration facilities of eastern states The number of tourists who suffer undiagnosed primary infections can only be imagined Fortunately the disease is almost always benign

An important problem often raised in non endemic areas is the question of contagiousness More fully discussed in Chapter Five it need only be mentioned here that man to man transmission of coccidioidomycosis has never been demonstrated No unusual precautions need surround the patient with coccidioidal disease in the non endemic areas Neither is there any evidence that new endemic areas have been created by the returning home of patients harboring the fungus

Coccidioidomycosis has not been an unmitigated hazard for non endemic areas for knowledge of *Coccidioides immitis* has advanced immeasurably the knowledge concerning other fungi particularly *Histoplasma capsulatum* For 40 years "Darling's Disease" was known only in its fatal disseminated form At the same time a vast incidence of non tuberculous pulmonary calcification among inhabitants of the Mississippi Valley was unexplained The two conditions were related and the mystery of histoplasmosis was solved when its striking analogy to coccidioidomycosis was noted The advance of the understanding of *Histoplasma* was almost a by product of the increasing knowledge of *Coccidioides* Students of the southwestern disease prepared the way for their colleagues in the middle west The resulting information has now diffused throughout Latin America and Europe where histoplasmin and coccidioidin skin testing surveys are exposing the unsuspected vastness of the histoplasmosis problem

*Chapter Two*

# The History of Coccidioidomycosis



## THE PRE-SCIENTIFIC PERIOD

HUMAN COCCIDIOIDOMYCOSIS is, as far as we know, a relatively new disease, for the areas where it can be contracted have been significantly populated only during the last century. Indian tribes and early European explorers must have been exposed in more distant times, but we have no knowledge of the disease among them then. The San Joaquin Valley of California, best known of the endemic areas, was once a sparsely inhabited desert where the Yokuts Indians hunted elk and antelope, geese and doves. If coccidioidomycosis visited native villages, it was incomparably more benign than the cholera, syphilis, and Spanish influenza which the white man introduced at the end of the eighteenth century, diseases which hastened fifty tribes of Yokuts into oblivion. When Spanish vaqueros settled on land grants in the southern San Joaquin Valley in 1845, they were pursued by smallpox and dysentery rather than by any recognizably new infection. The era of modern farming in the San Joaquin Valley really began when the railroad pushed southward from San Francisco in the middle 1870's. Not many years later it was realized that this vast agricultural empire spawned a new and deadly disease, coccidioidal granuloma, which was to give the Valley its unwelcome distinction.

The endemic areas of Arizona New Mexico and Texas were likewise but sparsely settled frontiers until fairly recently although coccidioidal infection probably existed among the Arizona Indians if modern epidemiologic studies reflect ancestral conditions[*] Except for primitive native tribes and isolated garrisons of Spanish soldiers the endemic areas of South America were also virtually uninhabited until the present century

## THE ERA OF DISCOVERY, 1891 1899

In 1891 a middle aged soldier from the Argentine Pampa was sent to the University Hospital in Buenos Aires because of an unusual tumor of the skin There he was studied by Alejandro Posadas a 21 year old medical student working in the pathological laboratory of Robert Wernicke A native of Argentina the patient had been in robust health until four years previously when he had noticed verrucous patches on his nose and right cheek then on his thigh and back At first no bigger than the head of a pin the nodules enlarged became ulcerated and looked Posadas said very like a cauliflower[13] Although he and Wernicke considered the lesion to be neoplastic—an example of mycosis fungoides—they clearly recognized therein a parasite which they likened to the protozoan *Coccidia* In 1892 Posadas published a preliminary report in Argentina[1] as did Wernicke in Germany[3] both unaware as yet of the malignant course the disease would follow In 1894 Posadas wrote his doctorate thesis on the same subject "A Contribution to the Study of Tumors"[4] In the next few years with temporary remissions the disease progressed until the patient s skin was everywhere covered by lesions the lymph nodes were generally involved and the viscera were full of miliary tubercles The changing picture was the subject of several of Posadas published studies[9,1 15] In 1898 after seven years of recurrent fever and painful new eruptions the patient finally died

Fifty years later in 1948 Dr Flavio L Niño Professor of Parasitology at the University of Buenos Aires School of Medicine was browsing through the anatomical museum of the medical school when he came upon an unidentified head perfectly preserved (Fig 1) Its appearance reminded him of Posadas description of the stricken soldier[6,14] Microscopic study of the skin lesions and comparison with Posadas photographs removed all doubt that Posadas patient had been rediscovered after half a century The next year a hand and foot were also found still teeming with embalmed parasites The specimen is now Exhibit No 1 in the Institute of Parasitology at the School of Medicine in Buenos Aires

About the same time that Posadas soldier developed his mysterious malady in Argentina an immigrant Portuguese farm laborer in California became similarly ill[6,8]

Joas Furtado Silveira, an ambitious young man of 33 years, came to the San Joaquin Valley from his home in the Azores in 1886. Within a year or so he noticed a tender spot on the back of his neck where his collar rubbed the skin. Similar patches appeared on the forehead. Although he was able to work for several years, his fellow laborers were so afraid of his ugly skin lesion that he had to room by himself. In 1893, when his strength had long since failed, he entered the San Francisco City and County Hospital to remain until he died in January 1895. Fungating skin lesions spread over most of his face and invaded the eyes, destroying his vision. The eruption was so sensitive that the slightest touch caused him to cry out in pain. Regional lymph nodes became swollen and fluctuant. Cough and purulent sputum increased. Rales filled the lungs. Abscesses appeared on the legs and in the testes. Despite frequent surgical debridement and the application of methyl violet, iodine, bromine, oil of turpentine, carbolic acid, potassium permanganate, and bichloride of mercury, he failed steadily and died about eight years after the appearance of the first skin lesion.



Figure 1. Anatomical specimen from Posadas and Wernicke's original case of coccidioidomycosis. (From Niño, *Boletin del Instituto de Clinica Quirurgica* 26:311, 1930.)

At necropsy, abscesses and tubercles were found in the skin, subcutaneous tissues, bones, testes, lungs, liver, peritoneum, spleen, lymph nodes, and adrenal glands. Microscopic examination of the lesions showed them to be filled with a parasite new to California physicians. Emmet

Rixford with the help of T C Gilchrist of Johns Hopkins Hospital studied the organism stained it and inoculated it into the skin of dogs and rabbits to produce local lesions and regional lymphadenitis [6] When they attempted a bacteriologic culture the plate was overgrown with a mold and was therefore discarded as contaminated At the suggestion of Dr Charles Wardell Stiles the eminent protozoologist they concluded that the organism was a protozoan of the class Sporozoa Because of its resemblance to the genus *Coccidia* the agent of coccidiosis in chickens they called it *Coccidioides immitis* ( im" not plus *mitis*" mild hence not mild severe or as Dickson put it savage [6])

In 1894 Dr W S Thorne of San Francisco had showed Rixford a second patient—also a Portuguese from the Azores who had worked in the San Joaquin Valley—whose illness was fatal in but twelve weeks after the appearance of the first skin lesion [7] Thinking the causative organism was slightly different from the one first seen Rixford named it *Coccidioides pyogenes* [8]

Rixford recognized that his cases were similar to that of Wernicke and Posadas although the final report of the latter was not published until four years later The paper of Rixford and Gilchrist published in 1896 [8] was the first extensive study of coccidioidomycosis and the first in which the significance of the parasite as the agent of a new and distinctive disease was appreciated

## EARLY MYCOLOGIC INVESTIGATIONS 1900 1913

In 1900 shortly before his own untimely death at the age of 32 Posadas published a more complete account of his case which had come to autopsy two years before and described the reproduction of the disease in monkeys and dogs [1] In the same year William Ophuls began the work which made him for a third of a century the foremost authority on coccidioidal disease With Herbert Moffitt he reported upon the third American patient also a Portuguese farm laborer from the Azores [14] This was the first case in which the whole course of the disease is traceable in retrospect from primary pulmonary infection to death with miliary dissemination three months later Although Ophuls noted the protozoa of Rixford and Gilchrist in pathological sections and in inoculated guinea pigs he discovered that culture of the organism always produced colonies of a mold Ophuls himself said that when Moffitt and May Ash first showed him the mold on the culture plates he considered it a contaminant until subcultures from guinea pigs regularly showed the same fungus Its life cycle was roughly outlined in this preliminary report the first systematic study of *Coccidioides*

The fourth American case was reported by Montgomery in the same year (1900)[17] and soon thereafter several others were described.[1, 19] In 1904 Wolbach described the morphology and cultural characteristics of *Coccidioides*.[20]

In 1905 Ophuls published his second and third papers on the disease, studies so carefully done that very little new could be added for thirty years. In one paper he described in detail its gross pathology, histology and clinical course, summarizing all the previously reported cases.[21] Contrary to previous opinion, he emphasized the primacy of the lung as the portal of entry of the fungus. In the other paper he delineated the biphasic life cycle of *Coccidioides immitis* and described its morphology in both the parasitic and saprophytic phases.

In the next nine years but few advances were made. New cases were diagnosed each year in California.[3, 4, 6, 31, 33, 34, 35] Hektoen noted the resemblance of the pathologic lesions of coccidioidomycosis to those of tuberculosis. Evans reported a case of meningitis without obvious disease elsewhere in the body.[8] Von Wasielewski reviewed the American studies in the first German paper on the disease. The first reported coccidioidal infection acquired in Texas, that of a young physician whose illness was rapidly fatal, was erroneously diagnosed blastomycosis[7] until MacNeal and Hjelm correctly identified the causative organism.[38]

## IMMUNOLOGIC AND EPIDEMIOLOGIC ADVANCES, 1914-1924

In 1914 and 1915 several classical studies were accomplished. Jean V. Cooke laid the foundation for the later studies of the immunology of coccidioidal infections when he demonstrated a specific precipitin reaction in a patient with granuloma.[40] He was unable to demonstrate skin sensitivity and complement fixation antibodies with the methods used. MacNeal and Taylor discussed the 24 previously recorded cases of coccidioidal granuloma and described in nice detail the development of the saprophytic stage of the organism from sporangia.[41] Using anaerobic cultures, they also devised the first method of perpetuating spherule multiplication in vitro.

In 1915 Ernest Dickson began the work which was to make him an authority second only to his senior colleague at Stanford University, William Ophuls. His first paper was a thorough clinical description of coccidioidal granuloma and an account of nine new cases, bringing the number of reported cases to 40.[42] In the same year the disease was again described in Europe by Campiche, whose patient had contracted the infection in California.[43]

In the next ten years the most noteworthy advance was the earliest descriptions of the roentgenological characteristics of coccidioidal disease

by Bowman[3] and Taylor[61] Lynch reported a case in South Carolina[7] Hirsch fearing that the disease was being introduced into Chicago described a fatal case which had originated in California[9] A new mycosis at first thought to be coccidioidal was reported in Brazil by Gomes and de Assumpção[63]

By 1925 as the first quarter of the century drew to a close awareness of the disease was widespread on three continents—North America South America and Europe Seeds sown one by one in various laboratories were about to bear fruit In the next four years more studies were to be published than in any previous decade The second quarter of the century opened with a flurry of investigative excitement that anticipated the epoch making discoveries of ten years later

## PATHOLOGIC AND MYCOLOGIC PROGRESS, 1925-1936

The years 1925 1936 brought to culmination the early pathologic epidemiologic and mycologic studies The fungus and its taxonomy were further studied by Bump[66] Castellani[7, 87, 103, 1] and Ciferri and Redaelli[13, 149, 1, 9-1, 1, 7] Montenegro described the first recovery of *Coccidioides immitis* from the blood[6] Coccidioidin skin sensitivity was demonstrated by Hirsch and his co workers[77, 86, 1, 4] and by Jacobson[93] Laboratory infection was reported by Tomlinson and Bancroft[9, 96, 197] Coccidioidal infection in farm animals was described by Beck[111, 134] Indigenous infection was noted in Texas[146, 147, 1] Cases were also reported although endemicity was not demonstrated in Mexico[149, 1] Kansas[7] Louisiana[199] Hawaii[2] Italy[130, 103] and erroneously in China[136] Florence Ahlfeldt in part collaborating with Riesman reviewed all published cases[68] demonstrated the pulmonary route of infection in guinea pigs[69] reported the first case in New Mexico[84] and described spores in tissues[93] Coccidioidal meningitis was studied pathologically by Rand[1] and Abbott and Cutler[18] Evans and Ball reported the first series of autopsies eighteen in number[107] The relationship of South American Blastomycosis was clarified and its early confusion with coccidioidomycosis gradually corrected by a series of studies those of de Almeida being most critical[99, 100, 117, 118, 141, 143, 16, 171, 174]

During this decade two observations anticipated in part the great discoveries of 1937 In 1929 Ophuls stressed the overwhelming evidence that the lung is the portal of entry showing that old primary pulmonary lesions are almost always demonstrable in coccidioidal granuloma[11] In 1932 Stewart and Meyer isolated *Coccidioides immitis* from the soil of a San Joaquin Valley farm where four Filipinos had contracted serious or fatal infections[1, 7]

## THE REAWAKENING, 1937-1940

The "Renaissance period in the study of coccidioidomycosis," to use Meyers' well-known phrase,[79] was the result of the work of two California physicians, Myrnie A. Gifford of Bakersfield and Ernest C. Dickson of Stanford. Dickson had long suspected that there was a milder, more common form of coccidioidomycosis than coccidioidal granuloma, but living in San Francisco, he did not have the opportunity to see such cases on an epidemic scale. In 1931 he wrote:

> Coccidioidal granuloma probably occurs with much greater frequency than has been believed. . . . The relatively high percentage of positive findings by Beck in a small series of beef animals and sheep (18.4 per cent) indicates that infection of human beings and certain animals in California cannot be unusual. . . . There have been at least three proved cases and five or six suspected cases in which the progression after pulmonary infection has not been rapidly downward but to apparent recovery. . . . It is suspected that this type of infection may be much more common than has been believed.[137]

The first clue to the benign form of coccidioidal infection came as the result of a laboratory accident in 1929. H. C. Chope, in his own right to become a recognized investigator of coccidioidomycosis, was then a medical student working in Dickson's laboratory. One day he opened a Petri dish containing an old culture of *Coccidioides* in order to examine it more closely. As his breath touched the colony, it exploded in a puff of fine spores, and he inhaled a lungful of the deadly cloud. Eight days later he was stricken with pleuritic pains so severe that his chest had to be strapped. He suffered fever, cough, hemoptysis, and a weight loss of 15 pounds in as many days. Chest roentgenograms indicated hilar lymphadenopathy and patchy bronchopneumonia. Four weeks later erythematous nodules erupted on his shins. Endosporulating spherules were seen in the sputum, and from it was cultured a fungus fatal to guinea pigs. A diagnosis of coccidioidal granuloma was made, and the worst was expected, but the pneumonia soon cleared and he recovered completely to spend a long vacation in Arizona at the expense of the medical school.[5, 79]

Four months later Dickson saw a second patient who recovered rapidly from coccidioidal pneumonia diagnosed by the finding of the fungus in the sputum. The only difference from his first case was that erythema nodosum did not occur. In neither patient did coccidioidal granuloma develop.[79]

In 1935 Dickson saw a young engineering student who, after working in the oil fields in western Fresno County, had an acute respiratory illness accompanied by erythema nodosum. Shortly thereafter a skin lesion containing *Coccidioides* appeared on his neck. Several other such cases con

vinced Dickson that coccidioidal granuloma is but the end stage of an infection which is caused by inhalation of chlamydospores" of *Coccidioides immitis* [9]

Just as Dickson was becoming highly suspicious of the existence of a mild form of coccidioidal disease Dr Myrnie A Gifford of the Kern County Department of Public Health began to suspect the same thing In August 1934 only five days after she had begun work in Bakersfield Dr Gifford saw a 45 year old white woman a fruit picker who had a severe acute pneumonia and erythema nodosum Dr Joe Smith the Kern County Health Officer told her that it was a case of "San Joaquin Fever a disease of unknown etiology very frequent in Kern County Three months later Dr Gifford saw a Filipino man of 26 years with a chest cold fever cough and erythema nodosum whose sputum contained *Coccidioides immitis* She began to wonder if there was a relationship between San Joaquin Fever and coccidioidal disease [61]

In January 1936 Dr Dickson visited Bakersfield in the course of his research on coccidioidomycosis While preparing for his visit Dr Gifford noticed that the records of three out of fifteen cases of coccidioidal granuloma mentioned antecedent erythema nodosum Dr Dickson was immediately interested in her observation recalling the laboratory acquired infection of Dr Chope which had also been accompanied by erythema nodosum In addressing the staff of the Kern General Hospital later that day Dickson mentioned Dr Giffords suggestion that San Joaquin Fever might be an early manifestation of coccidioidal infection Two other staff members then recalled having seen San Joaquin Fever preceding other cases of coccidioidal granuloma [30]

Six months later the Annual Report of the Kern County Department of Public Health for the Fiscal Year 1935 1936 [19] said

> Incomplete reports showed more than a score of cases of a hitherto unpublished disease popularly called San Joaquin or Desert Fever" which is characterized by early symptoms of bronchopneumonia followed in a week or ten days by raised reddened tender bumps" or nodules on the legs arms and sometimes on the chest neck and face this rash is sometimes diagnosed as "erythema nodosum" An x ray of the lungs in these cases usually reveals parenchymal and hilar lymph node involvement and sometimes pleurisy or pleurisy with effusion or interlobar empyema An x ray diagnosis of the chest findings in these cases is frequently tuberculosis" However there is usually complete recovery as shown by the x ray a few months later
>
> Research studies are being carried on by the County Health Department and the staff of the Kern General Hospital to determine the relationship if any of coccidioides to San Joaquin Fever The coccidioidin test in all cases of San Joaquin Fever" so far tested with the Kessel coccidioidin prep

aration has been so strongly positive that it has been found necessary to use it in one tenth dilution with normal saline to avoid temperatures and severe local reactions

To date the typical double walled capsules characteristic of coccidioides have been recovered by direct examination of sputum smears, cultures and by animal inoculations from six cases diagnosed as San Joaquin Fever or erythema nodosum

In May, 1937 Dickson read his paper, "Valley Fever of the San Joaquin Valley and Fungus *Coccidioides*" at the Del Monte Session of the California Medical Association, *suggesting the name "coccidioidomycosis"* for all stages of the disease and subdividing it into primary and secondary phases [9] Several other cases of primary coccidioidal pneumonia some progressing to fatal dissemination were carefully studied and reported by Drs Dickson and Gifford The conclusions of their definitive paper, [10] a classic study published jointly in the *Archives of Internal Medicine* were as follows

> It has been shown that infection with the fungus *Coccidioides* may cause disease of a primary or secondary progressive type
>
> *The primary form of the disease is due to inhalation of the chlamydospores formed in the vegetative phase of the growth of Coccidioides*
>
> Infection with *Coccidioides* is common in the San Joaquin Valley in California it is usually mild and the great majority of patients recover without complications
>
> The condition is often diagnosed as a bad cold or "flu" in the beginning but when erythema nodosum occurs in its course it is popularly known in the San Joaquin Valley as desert or valley fever
>
> In a few cases the condition subsequently progresses to the highly fatal disease known as coccidioidal granuloma
>
> The name coccidioidomycosis has been suggested to include *all types* of infection with the fungus *Coccidioides*

In September 1937 a grant was made by the Rosenberg Foundation in San Francisco for further study of acute coccidioidomycosis With this support there was undertaken as precise an epidemiologic study as has ever been made of any disease clearly defining the extent of the problem in the San Joaquin Valley indicating its generally benign course and revealing the conditions under which it is most likely to be acquired Scores of physicians nurses and interested laymen took part in the study but the leaders of the team were Dr Gifford Dr Dickson and a protege of the latter named Smith

Dr Charles E Smith was to become the third member of the Stanford dynasty of coccidioidomycologists succeeding William Ophuls and Ernest Dickson *He became Professor of Public Health at the Stanford University*

School of Medicine after Dickson s untimely death in 1942 At present he is Dean of the School of Public Health at the University of California and President of the California State Board of Public Health

From December 1937 to May 1939 Smith spent three days a week in Kern and Tulare Counties the southernmost counties in the San Joaquin Valley making an intensive survey of the incidence of Valley Fever [73] County health departments and medical societies practicing physicians nursing organizations private ranchers and governmental agencies co operated in the study In a year and a half Dr Smith saw 432 patients with erythema nodosum or erythema multiforme from 15 months to 70 years of age The fungus was recovered from the sputum of many and the coccidioidin skin test was found to be positive in all (except 15 who refused to cooperate) The incubation period was established at 7 to 21 days usually about 2 weeks The seasonal incidence was noted to be high in the summer and fall Most of the patients were newcomers to the San Joaquin Valley part of the vast influx of agricultural workers from the mid western states Although only cases with erythematous skin lesions were studied intensively it was soon apparent that only a small minority of patients with primary coccidioidomycosis developed dermatoses

Two other important papers appeared from Stanford University at this time Alvin J Cox Professor of Pathology and Smith reported four instances of arrested coccidioidal lesions of the lungs or bronchial lymph nodes in patients dying of other causes Typical spherules at least some of which were viable were seen in old encapsulated caseous partially calcified foci Similar lesions could be produced in experimental animals Harold K Faber Professor of Pediatrics together with Dickson and Smith published the first description in the pediatric literature of Valley Fever in children [8]

In August 1939 Drs Dickson Gifford and Smith reported their find ings to the Sixth Pacific Science Congress meeting at Berkeley and Stan ford [6, 61, 73] Their papers summarized so well the discoveries of the previous three years that most of the studies made since then have been merely refinements August 1939 marked the climax of the Renaissance period

## THE CONTEMPORARY PERIOD 1941 PRESENT

Once the general pattern of coccidioidal disease had been determined it was easy to work out lesser problems The decade between 1940 and 1950 offered unparalleled opportunities for studying the infection because of the large concentrations of non immune men in the military installations of endemic areas Charles E Smith appointed civilian consultant to the Secretary of War for the study and control of coccidioidomycosis in the

armed forces, completed several important studies concerning its epi ology and immunology With Rodney R Beard H G Rosenberger E G Whiting he showed that dust control in army air fields—by surfacing roads and air strips building swimming pools rather than at fields and planting grass in dusty areas—reduced the infection ra 65 per cent[4] He and his colleagues then described the varieties of cidioidal infection[4 3] and the patterns of coccidioidin skin sensitivity serological reactions in many thousands of cases[3 4 6 6] With Robe Peers and Emile F Holman he reported surgery for coccidioidal cavit With E E Baker and E M Mrak[313] he made an exhaustive stu morphology taxonomy, and distribution of the fungus His personal tacts with so many of the problems concerning the fungus have Smith the authority in the field

The experience of other physicians in the military service also a greatly to our knowledge Shelton reported a small epidemic at C Roberts California in an area not previously known to be endem Goldstein and Louie described the clinical features of the disease occurred in epidemic proportions in 75 soldiers who had been on biv near San Luis Obispo California[31 361] Colburn described the roentg logic findings in the same patients[3 5] Lee[36] Cheney and Denenl[31 3 0] Willett[3 4 5] Sweigert Turner and Gillespie[4 1] and several ot made extensive studies of the clinical aspects Jamison and Carter[4] Rakofsky and Knickerbocker[414] and others studied the roentgenolo tures Forbus and Bestebreurtje of the Army Institute of Patholo ported the pathologic findings in 95 cases the largest such series to da

Following World War II residual lesions in returning soldiers w described by a number of observers particularly by Bass Berke and t colleagues in New York[3 6 33 4 3 16 133 61 0 5 0] Individual cases of seminated disease appeared all over the United States Surgery for resid lesions was reported by Greer and his colleagues Weisel and Owe and Cotton and his colleagues[71 813] The question of contagion fr patients returning home was raised by Rosenthal but no clinical examp were noted[413 4 3 4 4 3 6 1 6]

In the same period many studies were made among civilians in demic areas William A Winn of Springville California in a series brilliant papers described the residual pulmonary cavity and its ben nature[3 341 311 6 3]

Other important studies were made in Kern and Tulare Counties Gifford Thorner Buss Birsner Huntington Smile Ramirez, Vaugl Cohen Maloney Levin Einstein Mead Mackler and others Emme and his co workers discovered the disease among rodents of Arizona

[3, 316, 317] where its endemicity had already been demonstrated by Phillips, Woolley, Farness, Mills[798] and Aronson.

Several instructive epidemics of coccidioidomycosis occurred in situations where ideal conditions for study obtained. First and best known of these was one reported by Davis, Smith and Smith in 1942, in which seven of fourteen university students and faculty members were stricken following a biology field trip from Stanford University to the Panoche Valley in San Benito County, California.[319] A reconstruction of the events of the three-day field trip indicated that the seven victims (and two immune companions) were in a group by themselves on only one occasion—when they pursued a rattlesnake to a squirrel hole and tried to dig it out. Dust flew so thickly that breathing was difficult. Within two weeks primary coccidioidomycosis appeared in all seven. Three months later, after all had recovered, one of the students guided Charles E. Smith back to the suspected rattlesnake hole, and *Coccidioides* was recovered from the soil. Powers and Stark reported the roentgenographic studies they made of the victims of this epidemic, recording for the first time the changes that occur in the lungs as the pulmonary reaction to *Coccidioides immitis* develops and recedes.[30]

In South America interest in the disease revived after nearly forty years. At first depending heavily on North American investigators, particularly on Charles E. Smith, research there became more and more independent. Cases were recognized with increasing frequency, coccidioidin surveys were made in most of the countries of Central and South America, and original mycologic studies were undertaken. Some of the leaders in Latin America are Gonzalez Ochoa of Mexico, Campins of Venezuela, MacKinnon of Uruguay, Gomez of Paraguay, and Nino and Negroni of Argentina.

It is harder to evaluate objectively the present decade. The years since 1950 have been primarily years of assimilation and diffusion of the previously acquired knowledge concerning the geographical distribution, epidemiology, ecology, and symptomatology of the fungus and its disease. New endeavors have been mainly concerned with two problems: (1) refinements of mycological knowledge and techniques, and (2) therapy of disseminated coccidioidomycosis.

Several groups of investigators have further clarified the mycology of the fungus. C. E. Smith continues this work at the University of California, as have his colleagues Lorraine Friedman, Demosthenes Pappagianis and Lee Gordon. In Los Angeles J. Walter Wilson, Orda A. Plunkett, Robert Lubarsky, Victor D. Newcomer, J. E. Tarbet, Edwin T. Wright, Alvin J. Leeb, Thomas H. Sternberg, Louis H. Winer and Carlyn Halde are making important contributions concerning both the mycology and treatment of

the disease Ruth C Burke of Yale Ralph A Vogel Norman F Conant and Heinz E Karrer of Duke and Libero Ajello and his co workers of the U S Public Health Service at Atlanta have also made new observations and devised new methods of mycologic study In Arizona revealing ecologic and veterinary studies have been accomplished by Keith T Maddy Raymond E Reed Charles J Prchal and others

Thomas F Puckett of Fitzsimmons Army *Hospital in Denver pointed* out the frequent occurrance of hyphal forms of *Coccidioides immitis* in the *human host*[819] *and Fiese Cheu and Sorensen of Fresno reported hyphal* forms in sputum of patients with coccidioidal cavities[8]

Research concerning treatment follows two main patterns In the east and middle west a number of therapeutic agents are being tried against various deep mycoses and coccidioidomycosis often appears as one among several diseases being treated experimentally I Snapper of New York[881] and Arthur C Curtis and his colleagues of the University of Michigan are leaders in this type of study

In Southwestern states research has been aimed more specifically at disseminated coccidioidomycosis Roger O Egeberg and his colleagues at the Los Angeles Veterans Administration Hospital have studied prodigiosin Robert Cohen of Bakersfield has reported the in vitro and in vivo effect of a variety of drugs which he has tried Fiese Ridding Cheu and Steinbach of Fresno[796, 8 1] and James L Dennis and Arild E Hansen of the University of Texas[70] have reported successful treatment of several cases with ethyl vanillate Charles E Smith and Lee A Gordon have made animal experiments with a number of the newer fungicides[86] Amphotericin *B has been tried by Sternberg and his colleagues at the University* of California at Los Angeles[941] and others[939]

Thus far therapy has lagged far behind the precise knowledge we have concerning other aspects of fungus *Coccidioides* The next few years are *faced with the anticipation that they will bring its control* That will be a fitting climax to the search begun by Posadas Rixford and Ophuls and brought nearly to completion by *Dickson Gifford and Smith*

*Chapter Three*

# Mycology of *Coccidioides immitis*



## MYCOLOGIC PRINCIPLES

FUNGI ARE simple plants, but a step higher than bacteria. Most of them are harmless saprophytes; a few cause disease in man, animals, or other plants. Fungi, together with algae, are classified in the *Phylum Thallophyta*—elementary plants not differentiated into roots, stems, or leaves. Algae, containing chlorophyl, are able to utilize the energy of sunlight to manufacture their own food by synthesis from carbon dioxide and water. Fungi, lacking chlorophyl, must depend on other living organisms for food and are therefore either saprophytic or parasitic.

Fungi are subdivided in large part on the basis of their types of reproductive cells or spores. Some, the yeasts, reproduce by simple budding of the parent cell. From the spores of most, germ tubes extrude to become

long branching filaments or hyphae, the tangled mat of which is called the mycelium The vegetative mycelium penetrates the substrate and absorbs food The aerial mycelium projects above the surface and bears the reproductive cells The *mycelium and its spores represent a primitive* plant or thallus The hyphae of certain species become subdivided into chains of cells by cross walls or septa Some of the cells become specialized reproductive cells, the spores Ascospores are sexual spores (i e spores produced by nuclear fusion) contained in an ascus or spore sack Thallospores are asexual spores borne on the hyphae One *type of thal*lospore, the chlamydospore is an enlarged round thick walled spore borne at the end of a hypha (terminal), in the middle (intercalary) or on the side (*lateral*) *A similar type of thallospore* the arthrospore is a rectangular thick walled segment of the hypha Sporangia are spore containing swollen structures usually seen on the ends of the hyphae of phycomycetes

Colonies of fungi may be described as yeasty, yeastlike and filamentous The first composed of single celled budding forms are soft moist, *membranous colonies like those of bacteria Yeastlike colonies have the* same appearance but contain a vegetative mycelium Filamentous or mold like colonies have fluffy powdery or cottony aerial mycelia

Some of the pathogenic fungi present different appearances as saprophytes and parasites having different life cycles in the tissues and in external nature

There are several slightly different schemes by which fungi are classified In general the true fungi are subdivided into phycomycetes ascomy*cetes basidiomycetes and a fourth group sometimes called hyphomycetes* and sometimes with a slightly different implication fungi imperfecti The place of *Coccidioides* in the scheme depends on definition Except for the schizomycetes almost all pathogenic fungi are included in the fourth group

## MYCOLOGIC CHARACTERISTICS OF *COCCIDIOIDES IMMITIS*

*Coccidioides* is a genus containing but one species *Coccidioides immitis* Rixford and Gilchrist *1896 It exists in two distinct phases the* saprophytic and the parasitic (Fig 2) The former occurs in external nature on laboratory media, and in host tissues under certain conditions which approximate external nature The latter occurs in animal tissues and under certain laboratory conditions in which living tissue is more or *less mimicked*

### Taxonomy

The taxonomic position of *Coccidioides* is not clearly defined because the organism has characteristics which cause difficulty with any of the

standard classifications Opinion differs more about *Coccidioides* than about any other pathogenic fungus Early investigators considered the spherule to be an ascus and the fungus therefore an ascomycete There is fairly general agreement now that the spherule is not an ascus for endospores develop by cleavage and their number varies greatly not by multiples of two The present uncertainty is whether Coccidioides should

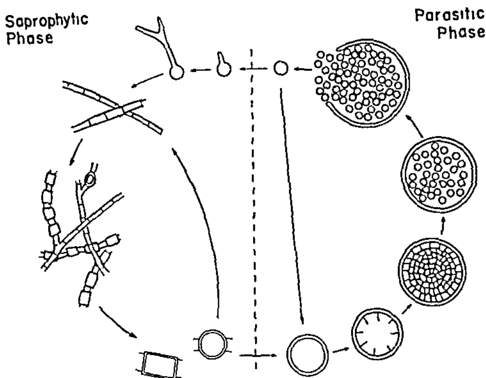



Figure 2 Diagrammatic representation of the life cycle of *Coccidioides immitis* saprophytic and parasitic phases

be classed among the phycomycetes or among the hyphomycetes or fungi *imperfecti Opinion is based on varying definitions* Castellani and several later mycologists included *Coccidioides* among the fungi imperfecti or hyphomycetes [7] Conant classified it thus together with other fungi which do not have a sexual stage and which are not clearly phycomycetes ascomycetes or basidiomycetes C F Smith[180] and Emmons[3] considered it most likely a hyphomycete On the other hand Baker Mrak and Smith with a somewhat stricter definition of fungi imperfecti stated that it is impossible to include Coccidioides in this group because it does not form conidia in its saprophytic phase and forms sporangia in host tissues [347] *These*

authors preferred classification with the phycomycetes despite the fact that *Coccidioides* has a consistently septate mycelium in the saprophytic phase unlike other phycomycetes They noted that Ciferri and Redaelli had already suggested the relationship to the phycomycetes [1] Negroni has restated this viewpoint on the basis of observations of endospore formation by means of the Wood's light [44] Blank and Burke[75] also suggested classification with the phycomycetes The question remains to be settled and is essentially academic

## Parasitic Phase

In infected tissue *Coccidioides immitis* appears as a round doubly walled structure commonly called the spherule (Fig 3) Formerly thought to be an ascus it is now generally considered to be a sporangium

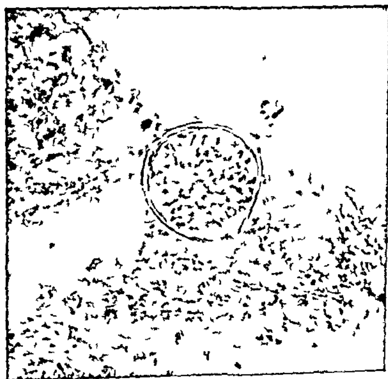


Figure 3 Doubly-contoured endospore-filled spherule of *Coccidioides immitis* in sputum (Reprinted from Conant *American Review of Tuberculosis* 61:690-701 1950)

When mature it contains globular or irregular endospores or sporangiospores from a few to several hundred sometimes disposed peripherally and sometimes throughout the spherule Its doubly refractile wall is about 2 micra thick The thin inner wall appears to be composed of

chitin [4] The thick outer wall has an exterior layer of phospholipid [175] Ordinarily the spherule wall is smooth but sometimes it is covered with fine excrescences called "prickles and sometimes by club shaped protrusions 2 to 5 micra long

Figure 4 Young spherules of *Coccidioides immitis* before appearance of endospores (From Tarbet Wright and Newcomer *The American Journal of Pathology* 28 901 917 1952 )



Figure 5 Spherule of *Coccidioides immitis* in cleavage (From Tarbet Wright and Newcomer *The American Journal of Pathology* 28 901 917 1952 )

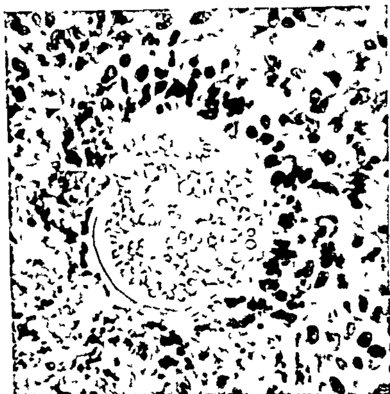
Most spherules measure 10 to 80 micra in diameter. Now and then one is larger—200 micra or more.[33] Endospores are usually 2 to 5 micra in diameter but occasionally reach 30 to 40 micra. Young spherules, more commonly seen than mature specimens, have clear cytoplasm without granules or endospores (Fig. 4). Formation of small nuclei in the develop-



Figure 6. Mature spherule of *Coccidioides immitis* filled with endospores. (From Winn, Coccidioidomycosis, in Hinshaw and Garland, *Diseases of the Chest*. Philadelphia and London, W. B. Saunders Company, 1956.)

ing spherule was reported by Emmons[1] and by Baker, Mrak and Smith[343] and was further studied with the electron microscope by O'Hern and Henry.[319] Cytoplasm divides by cleavage planes to form endospores (Figs. 5 and 6), which are liberated from the mature spherule by rupture of its wall (Fig. 7). Each endospore develops into a new spherule. The cycle is repeated indefinitely until brought to a halt by the defense mechanisms

Figure 7 Rupturing spherule and extruded endospores of *Coccidioides immitis* (From Baker and Braude *The Journal of Laboratory and Clinical Medicine* 47 169 181 Feb ruary 1956 )



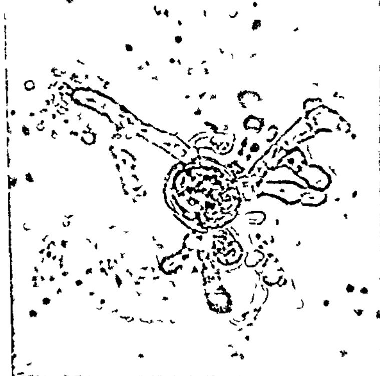


Figure 8 Germ tubes sprouting from spherule of *Coccidioides immitis* (From Baker and Braude *The Journal of Laboratory and Clinical Medicine* 47 169 181 February 1956 )

of the host or until the spherule is extruded from living tissue Some investigators have reported evidence that spherules conjugate prior to sporulation [150, 18] this could not be confirmed by Baker and Mrak [71] Spherules in apparent conjugation are seen so rarely that the appearance is probably an artefact Budding of spherules has also been described by some [101, 9] but conjugation and budding are thought by most investigators merely to be the close approximation of spherules which have developed from adjacent endospores or arthrospores [4, 9]

The spherule was the first known form of the fungus being described by Posadas [2] Wernicke [3] and Rixford and Gilchrist [8] when it was still thought to be a protozoan Ophuls who first demonstrated the vegetative filamentous phase noted the development of hyphal elements into spherules when injected into a guinea pig [14] Wolbach also reported chains of enlarged rounded hyphal cells in rabbit tissues 48 hours after injection [9] Ophuls held that culture material is not infective unless chlamydospores are present [77] an opinion in which Stewart and Meyer concur [31] Dickson reported that Chope on the other hand was of the opinion that immature cultures with neither chlamydospores nor arthrospores can also produce spherules when injected [8]

Tarbet Wright, and Newcomer have graphically described the changes in both the parasite and the host tissues at from 4 hours to 14 days after intraperitoneal injection of mycelium into mice [71] By 4 or 6 hours a few of the rectangular hyphal cells become enlarged spherical basophilic and thick walled During the first 48 hours these rounded hyphal spores or young spherules remain joined together in the hyphal chains By 96 hours most of the mycelium degenerates and disappears only a portion of its cells becoming spherules Young spherules grow larger until at 5 to 7 days they average 40 micra in diameter ranging from 15 to 90 micra Cleavage begins at this stage with the appearance of radial partitions Endospores thus produced are at first sharply angular and later round Mature spherules contain hundreds of endospores By the seventh day ripe spherules begin to rupture liberating their endospores From this time on new generations of spherules are encountered in all stages of maturity Mature spherules are usually contained in giant cells or histiocytes of the host

## Saprophytic Phase

The parasitic phase is terminated and the saprophytic phase begun by the death of the host or by the *expulsion of the spherule* from living tissue in sputum pus or exudates Conversion from one phase to another is not necessarily immediate for if conditions are not optimum spherules may apparently persist for a long time in sputum Rosenthal

has reported that spherules remained viable and infectious in exudates for over three months at refrigerator temperatures.[61] His experiments with sputum kept outdoors in sun or shade were less conclusive but it appeared that spherules could live for several days in the shade. Hampson observed

Figure 9. Chain of arthrospores of *Coccidioides immitis*. (From Tarbet, Wright, and Newcomer: *The American Journal of Pathology* 28:901-917, 1952.)

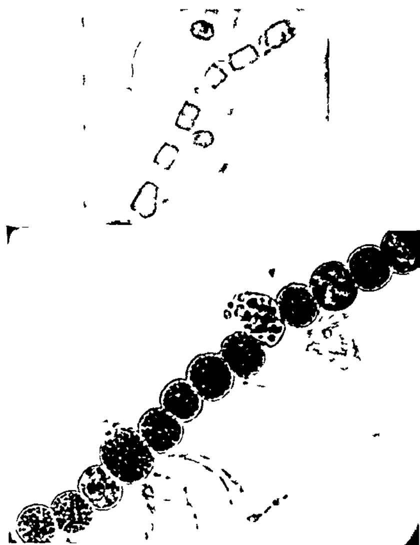


Figure 10. Chain of endospore containing spherules of *Coccidioides immitis* developing *in vitro* from mycelia culture spherules. (From Converse: *Journal of Bacteriology* 72:784-792, December 1956. U.S. Army Photograph, by permission.)

that spherules refrigerated for 15 months produced typical colonies when finally cultured.[80] When planted on artificial culture media, immature spherules and endospores, either free or still imprisoned, begin to germinate within 3 or 4 hours. Germ tubes sprout from the spherules and endospores to produce hyphae (Fig. 8). Branching and septation appear very early. By the second day the mycelium is tangled and complex. Young hyphae are 2-4 micra thick and have septa at regular intervals. By the end of a week many of the cells of the aerial mycelium develop into hyphal spores, usually rectangular (arthrospores) but sometimes round or ovoid (chlamydospores). Typical hyphae consist of barrel-shaped fertile arthrospores alternating with smaller sterile cells—the "empty cells" of North American mycologists or "disjunctors" of Negroni (Fig. 9).[101] Empty cells rupture easily to free the arthrospores, leaving on the latter tags or ornaments which help to distinguish the species. Hyphal chains thereby disarticulate readily, particularly in older cultures, so that the whole mycelium may disintegrate into a cloud of air-borne spores. Transverse dimensions of the hyphal spores are from 2 to 8 or 10 micra. Only occasional strains bear larger spores, up to 20 micra wide. With such tiny dimensions they are carried by the slightest breeze and, when inhaled, penetrate to the smallest bronchiole or pulmonary alveolus. When arthrospores or chlamydospores are placed on fresh media they sprout germ tubes which develop into new mycelia after the manner of endospores. Hyphal cells and spores contain one or two nuclei. Large chlamydospores may contain four.

Some observers have described special reproductive hyphae, distinct from the ordinary vegetative hyphae, alternately bearing spores and empty cells.[3, 101] Emmons reported the development in young cultures of specialized side branches almost twice the diameter of vegetative hyphae. Alternate cells delimited by septum formation increase in size, turgidity and mural thickness. Intervening cells gradually lose their cytoplasm but their walls persist to maintain the integrity of the chain until the occurrence of the disruptive sequence mentioned previously.

In addition to arthrospores and chlamydospores, another type of reproductive cells is sometimes borne by mycelia, the "culture spherules" of Baker and Mrak[11] or "sporangia" of Burke.[64] As early as 1914 MacNeal and Taylor observed temporary spherule growth and multiplication in media consisting of ascitic fluid or gelatinized horse serum containing sterile kidney slices.[11] However, MacNeal and Taylor were merely perpetuating the growth phase already existing, i.e., the parasitic phase, for their inoculum consisted of spherules in pus from infected animals. Their experiment was successfully repeated by Ciferri and Redaelli in 1936, who confirmed the development of endosporulating spherules from pus containing immature spherules.[3] The tissue phase has been cultured in embryonated

and non-embryonated eggs.[391, 571, 611] Lack in 1938 first showed that spherules sometimes appear in the mycelial or saprophytic phase.[46] Using a medium of beef infusion broth containing partially coagulated egg albumin incubated at 37 C under semi-anaerobic conditions, he observed that chlamydospores enlarged into round, doubly encapsulated bodies in which endospores formed. Baker and Mrak showed that certain strains of *Coccidioides* will bear the same type of reproductive cells on a variety of media at normal temperatures and under aerobiosis with no attempt to mimic conditions of the animal body.[91] These cells, which they termed "culture spherules," closely resembled spherules in animal tissues except that they were smaller (10-20 micra in diameter) and were not free, being joined to the hyphal chain in either terminal or intercalary positions.

Schlumberger observed the development of "culture spherules" from mycelia in citrated blood or horse serum incubated at 37.5 C in the slowly revolving tubes of a roller apparatus designed for tissue culture.[397] Burke induced the development of "culture spherules"—or, as she prefers, "sporangia"—at room temperature in a complex medium containing even coconut milk.[84] She observed that when endospores were released from the bursting sporangium they either grew into mature spherules directly or sprouted to form hyphae which in turn bore culture spherules or sporangia. Lubarsky and Plunkett also grew spherules in a CO-O atmosphere using another complex mixture which included rooster serum and tissue culture medium.[864] Dennis and Hansen were likewise able to produce spherules in living tissue cultures in a perfusion-type chamber. They noted that spherules and hyphal forms developed concurrently, i.e., the saprophytic and parasitic cycles occurred side by side with interconversion one to another. Converse[818, 809] was able to produce long chains of "culture spherules" (Fig. 10) in a liquid medium incubated at 37 C in complete darkness under reduced aeration.

Conant and Vogel discovered that they could alter the growth characteristics of certain strains of *Coccidioides immitis* for several generations by treating mycelia with Tween 80, a wetting agent.[789] Subcultures of all strains lost, to a great extent at least, their ability to form arthrospores. In some strains endosporulating culture spherules appeared in place of the arthrospores usually borne. Colonies were moist and yeast-like with little tendency to produce an aerial mycelium.

Baker and Braude noted that spherules were produced in vitro when living neutrophiles were added to suspensions of mycelial fragments.[891] They postulated two phases in the development of spherules from mycelia: (1) inhibition of mycelia by obstruction of the growing tip of the hypha and (2) emergence of spherules from the stunted mycelia in the presence of living neutrophiles. It was proposed that spherule formation is a mechan-

ical phenomenon in which attacking neutrophiles counter every advancing hyphal tip preventing mycelial growth and forcing development of the more resistant spherule They noted in vivo mycelial formation only in situations in which there is absence of leukocytes i e walled off pulmonary cavities and acellular meningeal foci

The demonstration of spherules in the saprophytic cycle showed that the two phases of *Coccidioides* are not necessarily mutually exclusive Baker Mrak and Smith *suggested that the complete saprophytic cycle* includes the culture spherule and the cycle usually seen without spherules is incomplete[313]

One might postulate that there are two normal types of vegetative reproductive cells—arthrospores (or chlamydospores) and sporangia which might be variations of the same cell Under certain conditions, the undifferentiated hyphal cell may develop into the arthrospore or chlamydospore and the latter into the sporangium At any stage development may take *one of several directions depending on conditions The chlamydospore* may sprout hyphae, or it may enlarge into an endosporulating sporangium The endospores of the latter may also either sprout hyphae or grow into endosporulating spherules Certain strains naturally tend to follow one pattern but presumably all strains are capable of following almost any pattern if conditions are right

Furthermore certain conditions foster certain patterns The young culture on artificial media tends to follow the saprophytic cycle In the living animal body the same strain follows the parasitic cycle" In between are borderline conditions in which both cycles occur side by side and interconvert one to another i e, in Lack's medium Burke's medium tissue culture etc Individual strains may naturally (in the old cultures of Baker and Mrak) or artificially (after "Tween 80") tend to follow both cycles concurrently

In recent years the frequent occurrence of hyphal elements in host *tissues has been appreciated* Two types of coccidioidal lesions *the residual* pulmonary cavity and benign pulmonary granuloma tend to harbor *Coccidioides immitis* in its mycelial phase* Sporadic instances of this phenomenon have been reported by Forbus and Bestebreurtje[4] Barnes (discussion of Bass)[3] Greer[2] Weisel and Owen and Seabury Peabody and Liberman Reviewing the first extensive series Puckett found hyphae of *Coccidioides immitis* in 73 per cent of 34 cavities and in 30 per cent of 30 pulmonary granulomas[319] Fiese Cheu and Sorensen demon

* There may be rare exceptions Baker and Braude report the finding of mycelia in the center of an avascular focus in the thick plastic meningeal exudate of a patient dying of coccidioidal meningitis[29] I have also seen an example of meningeal mycelial growth but whether it occurred ante mortem or immediately post mortem could not be determined with certainty

striated hyphae in the sputum of patients with coccidioidal cavities as well as in their surgically removed specimens (Fig 11)[8] Mycelial forms are most likely to be found on the surface of a cavity wall or within the necrotic debris of a granuloma i e not in the parenchyma of living tissue but in the borderline zone Sometimes both spherules and hyphal elements are found in close approximation At times hyphae contain intercalary spherules like the culture spherules of Baker and Mrak By the use of cavities produced artificially in rats (pneumodermas and granuloma pouches) Wright Newcomer and Sternberg experimentally produced hyphal forms in host tissues[9,11] These observations show that borderline conditions in which vegetative and parasitic phases develop side by side occur naturally in animal tissues as well as artificially in culture The surface of a pulmonary cavity is more like the surface of a culture medium than it is like the parenchyma of the lung the spleen or bone marrow It is to be expected that mycelia might grow in such a cavity and that hyphae might occasionally be found in its discharges

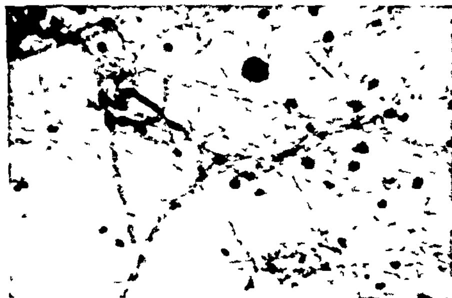


Figure 11 Branching septate hyphae of *Coccidioides immitis* in fresh sputum of a patient with a coccidioidal cavity of the lung Hotchkiss McManus stain (From Fiese Cheu and Sorensen *Annals of Internal Medicine* 43 255-270 August 1955)

Just as some strains tend more than others to produce spherules in culture so some may possibly tend to produce hyphae in host tissues The latter possibility is less susceptible to experimental proof than the former

## Gross Morphologic Characteristics

At room temperatures and on a wide variety of laboratory media *Coccidioides* grows faster than most pathogenic fungi. The thallus develops on solid media after inoculation with material containing spherules (either tissue or culture spherules), endospores, chlamydospores, or arthrospores. Growth is not clearly visible until the third to fifth day, when a moist flat membranous colony appears. In the next few days a fluffy white aerial mycelium typically develops, looking much like the surface of a cotton boll. At ten days the typical colony presents a central tuft of hyphae surrounded by a narrow zone of sparse growth and a wider zone of thick tangled cottony mycelium (Fig. 12). Enlarging gradually, the colony often fills a Petri dish in a month or so. It grows in either light or darkness, with no consistent differences. As it ages it turns tan and then brown and its surface becomes powdery with fragmented hyphae and free arthrospores.

## Variations Among Strains

*Morphologic Variation.* As inferred previously, there is considerable variability in the morphology—both gross and microscopic—among different strains of *Coccidioides immitis*. There is no evidence of significant variation in the antigenic properties of the fungus, even when obtained from widely separated parts of the world, so that there is no reason to postulate more than one species. *The morphology, however, is much less uniform.*

Variation within a species is, of course, almost the universal rule. It *is well known that variation occurs even in pure cultures of a single strain* of many fungi. Cultures derived from separate single spores of a parent *colony may differ morphologically.*

Baker, Mrak, and Smith reported striking gross morphologic differences among 15 strains of *Coccidioides immitis* from different parts of the world.[343] Colonies ranged gradually from flat and smooth to convex and cottony. Under the microscope there was less morphologic variation, although several strains tended to produce "culture spherules" in old cultures. In the parasitic phase there were no detectable differences. Antigenic characteristics were likewise apparently identical in all.

In a more comprehensive study of 47 strains of known pathogenicity Friedman and her co-workers demonstrated an even wider range of variation both grossly and microscopically.[1] Some strains produced either colonies or hyphae so bizarre that the morphology gave no hint of their identity. Furthermore, the confusion was multiplied by the use of various culture media. On one medium a strain *might produce a typical colony,* whereas another medium, which caused no change in most strains, might profoundly alter the *morphology or color of the strain* under considera-

tion Most strains on most media produced colonies which were at first moist membranous and flat and which soon formed an abundant white cottony aerial mycelium which became tan with age About a third of

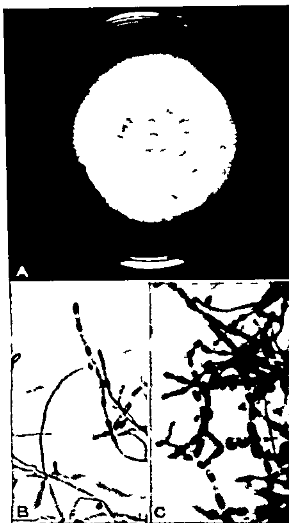



Figure 12 *Coccidioides immitis* A Culture on Sabouraud s glucose agar nineteen days at room temperature B Arthrospore formation in young culture x 580 C Arthrospore formation in old culture x 700 (From Conant *et al* *Manual of Clinical Mycology* 2nd Ed Philadelphia and London W B Saunders Company 1954 )

the strains however produced mature colonies which were unusual in color (yellow beige or dark brown) or in form (from flat and wet to rough and dry )

Under the microscope most strains showed varying numbers of the usual rectangular or ovoid spores, either free or in chains. Some strains however produced grotesque spores of varied size. A few produced none at all on any standard medium. All strains killed mice and the spherules of all looked exactly alike.

Hampson showed that sporulation of certain strains is depressed if screw caps instead of cotton plugs are used on test tubes, particularly if incubated at 37 C instead of at room temperature.[806] Friedman and Pappagianis have demonstrated that sporulation is inhibited if peptone is included in the medium.[90] Conant and Vogel discovered that "Tween-80," as mentioned previously, regularly depresses sporulation capacity for several generations and induces some strains to form culture spherules instead of arthrospores.[789]

The variability among different strains of *Coccidioides immitis* presents an obvious difficulty in diagnosis, for morphologic characteristics, either gross or microscopic, cannot be entirely relied upon. The spherule is the only morphologically constant cell. Definitive diagnosis from the mycologic standpoint therefore depends upon animal inoculation and recovery of the characteristic non budding doubly refractile endosporulating spherule.

***Variations in Pathogenicity.*** Although it is not possible to determine precisely the pathogenicity of different strains of *Coccidioides* for the human host, considerable differences of virulence have been shown in experiments with mice. Friedman and her co-workers have carefully studied 27 strains of *Coccidioides* from different parts of the western hemisphere and from a variety of clinical types of coccidioidal disease, all the way from mild primary pulmonary infections to fulminating dissemination.[illegible] Virulence determined by the relationship between a constant dosage of *Coccidioides* particles and the time of death varied from 100 per cent mortality within 30 days to 100 per cent survival through 90 days. There appeared to be no positive correlation between virulence for mice and that for men. The strain most lethal for mice was isolated from a patient with primary coccidioidal erythema nodosum from which recovery was complete. Some of the strains least virulent for mice were derived from fatal human infections. In general the more virulent strains were those whose hyphae produced typical arthrospores on solid media. Most of the strains, even those of low virulence, were highly infective.

## Physico-Chemical Characteristics

***Biochemical Characteristics.*** Cultural requirements of *Coccidioides* have been fairly extensively studied for many years. Although there have been minor points of disagreement among investigators, knowledge is in general certain.

Being a fungus in its natural state it requires some sort of an organic substrate or a substitute but very simple compounds will do It cannot fix nitrogen from the air but requires only a small amount in the medium and a wide variety of nitrogen containing substances are satisfactory—not only proteins but also peptone urea amino acids amides ammonium salts nitrates and others [311] Amino acids and ammonium lactate but not urea may be used as the source of both nitrogen and carbon at the same time [1] Proteolytic activity is moderate Milk is coagulated and peptonized and gelatin is liquefied in about 20 days [78] Keratin (hair and feathers) is di gested [129] Blood is hemolyzed Nitrates are not reduced to nitrites [403] Indol and hydrogen sulfide are not produced from animal proteins [403] Ammonia is formed particularly in acid media [66]

Carbon is likewise usable from many simple as well as complex sources—fats acetic acid and other organic acids (but not formic) amino acids and amides lactates hexoses disaccharides trisaccharides glucosides polysaccharides and alcohols [311] Not all are utilized equally well Carbo hydrates although good sources of carbon are not required as such and are not fermented with the production of acid and gas [311] Magnesium is indispensable although iron may be omitted [417] Vitamins and other growth factors are not required [417]

*Physical Requirements* The vegetative form of *Coccidioides immitis* is essentially an obligate aerobe although it will grow slowly in semi anaerobiasis [68] It is not fastidious as far as pH is concerned growing well with a pH variation of 2 to over 12 so that it can easily stand the extremes of pH in the soil [66] It withstands drying better than most organisms re sistance to dessication must be an important factor in the dissemination of dust borne chlamydospores Burke has reported its isolation from a seven month old sealed microscope slide [783]

Temperature tolerance is wide Dry spores remain viable for at least six months at −15 C [977] Exposure to a temperature of 46 C for two hours does not harm the fungus but it is killed in 4 minutes at 60 C and 95 per cent of viable cells are killed at 52 C in two hours [417] It grows at 22 C though not so well as it does at 37 C About 30 C is optimum for growth [403]

In brief *Coccidioides immitis* is not at all particular about its en vironment either chemical or physical It can subsist on simple organic compounds and even on inorganic compounds It will grow well on de cayed wood strips of carrots potatoes strips of cactus or even warm moist soil remaining viable for long periods It is therefore ideally suited for hot arid climatic conditions

## METHODS OF MYCOLOGIC STUDY APPLICABLE TO *COCCIDIOIDES IMMITIS*

Although once isolated *Coccidioides* may be grown with ease, its culture cannot be approached casually. Unless properly respected it is elusive and dangerous.

### Collection and Preparation of Specimens

*Concentration Procedures.* Methods slightly different from those used for bacteria are required for handling *coccidioidal materials. It has long* been recognized that concentration procedures appropriate for the study of the tubercle bacillus are lethal to *Coccidioides*. Ajello, in a well planned quantitative study, demonstrated that treatment of clinical specimens with sodium hydroxide, sulfuric acid, or trisodium phosphate usually destroys *Coccidioides* and several other pathogenic fungi.[67] Smith has proposed an alternative method for concentrating sputum, gastric contents, or contaminated pus.[307] The material is treated with cupric sulfate (0.05 per cent solution final concentration). Gastric contents should previously have been neutralized. After it has been allowed to stand for 4 hours the suspension is centrifuged. The sediment may be examined immediately under a cover slip, may be cultured on selective media, or may be inoculated into a guinea pig.

*Alkaline digestants* are sometimes useful in preparation for direct microscopic study even though they kill the organism. Cover slip preparations may be made by mixing a drop of pus with a drop or two of sodium or potassium hydroxide (10-30 per cent). For larger amounts the *material may* be placed together with twice the amount of 4 per cent sodium hydroxide in a 50 cc centrifuge tube, which is put in a boiling water bath for five minutes and stirred occasionally with a glass rod. It is then centrifuged for 20 minutes. The supernatant fluid is decanted and the sediment resuspended in 2 cc of distilled water. A loopful of the mixture is studied microscopically under a cover slip.

*Sputum.* The most useful specimen of sputum for mycologic study is often one collected soon after the patient awakens in the morning, for it represents pulmonary secretions accumulated during the night. It is helpful if the patient cleanses the mouth and teeth *before producing* the specimen. It must be certain that the material comes from the lungs and not from the mouth or nasopharynx. Several very deep breaths will often cause the patient to cough up secretions from far down in the bronchial *tree*. Sterilized Petri dishes are much better than the common hospital sputum cup for collecting the specimen. Material produced by a single paroxysm of coughing is far more likely to be diagnostic than a timed

collection of saliva food particles and nasopharyngeal hawkings Positive samples are often easily obtained after several failures if the physician himself will supervise the collection

*Discharges* *Coccidioides* can usually be recovered from purulent lesions especially if previously unopened and uncontaminated Spherules are often seen if a drop of pus is mixed with a drop or two of sodium or potassium hydroxide on a glass slide covered with a cover glass and examined under subdued light Even if the lesion is contaminated the fungus can be selectively cultured on cycloheximide medium

*Gastric Washings* Gastric lavage is not often either necessary or helpful In symptomatic primary coccidioidomycosis serologic tests usually give the answer so that even sputum studies may not be necessary In disseminated disease the peripheral lesion is almost always productive of diagnostic material In residual pulmonary cavities sputum studies usually suffice In solid residual pulmonary lesions where help is most often desired neither sputum nor gastric washings are likely to contain the fungus Consequently the range of usefulness of gastric lavage is not wide Furthermore it is not so likely to be productive of the causative organism as it is in tuberculosis *Coccidioides* is digested by gastric juice more readily than the acid fast organism so that even if any fungus elements remain at the time of aspiration they soon disappear unless rapidly cultured Usual concentration procedures as mentioned above destroy *Coccidioides* Nevertheless gastric lavage is now and then effective so that it may be worth while in some cases of undiagnosed pulmonary lesions to culture gastric aspirates on mycologic media as well as on media used for the tubercle bacillus The cupric sulfate method of Smith may be used for concentration

*Bronchial Washings* Material obtained during bronchoscopic procedures may also be cultured for *Coccidioides immitis*

*Biopsied Tissues* Surgically removed specimens may be stained by the methods hereinafter described and may be cultured or inoculated into animals Bain has described the demonstration of the fungus in a surgically resected lung specimen which was ground in a mortar digested with two volumes of 4 per cent sodium hydroxide for 30 minutes neutralized to pH 7 with 8 per cent hydrochloric acid and centrifuged The sediment contained many spherules[8,10]

*Spinal Fluid* Even in known cases of coccidioidal meningitis it is notoriously difficult to culture the organism from the spinal fluid Centrifugation may help to concentrate organisms and make culture more likely Wayne and Juarez have described a method for isolation of *Coccidioides* by use of a molecular filter membrane[8,7] The suspected spinal fluid 5 to 15 cc is passed through a sterile membrane (47 mm grid marked HA

type Millipore filter, preferably black, in a Pyrex filter holder*) and followed by a 10 cc. sterile distilled water wash. The membrane is then placed on brain heart infusion agar, *inoculated side up*, in a screw-capped 2 ounce jar. The jar is inverted, screwed into the cap in which is a sterile bibulous paper disk wet with 2 cc. of water, and *incubated at 37° C. or* at room temperature. Colonies are detectable in 3 to 6 days.

If infected spinal fluid is left at room temperature *in a cotton-plugged* test tube for a month or so, a cottony growth often appears on the surface.[16]

*Soil.* *Study of soil is of epidemiologic*, not clinical, significance, but the appropriate methods will be mentioned here. Stewart and Meyer, who first successfully isolated *Coccidioides* from the soil, mixed soil and brine into a paste which was allowed to percolate into a tall, narrow cylinder containing 30 per cent salt solution.[1] Fungus spores rose to the surface. Diluted supernatant fluid was centrifuged and the sediment inoculated into guinea pigs or cultured on a selective medium.

Ajello and his co-workers[8,9] have described a modification using currently available antibiotics. About 10 Gm. of soil is suspended in 30 cc. of physiologic saline containing 5,000 units of penicillin and 1,000 units of streptomycin per cc. The solution is stirred vigorously and allowed to settle for an hour. 1 cc. aliquots of the supernatant fluid are then injected intraperitoneally into each of 4 mice. After eight weeks the mice are *sacrificed and portions of liver and spleen inoculated into tubes of neutral* peptone dextrose agar, which are observed for six weeks.

*Air.* *On at least one occasion Coccidioides has been recovered* from dust-laden air, using an Anderson sieve sampler, in which air-borne particles were impinged directly on the surface of modified Sabouraud's media in Petri dishes.[91]

## Direct Microscopic Observation of Infected Material

*Although study of fresh, unstained sputum or other materials* is often *unrewarding, and identification usually requires* culture and animal inoculation, *sometimes the typical spherules of Coccidioides* are found by direct microscopic examination. In cases of pulmonary cavitation there may be found in the sputum tiny flecks, not unlike the "sulfur granules" of actinomycosis, which under the microscope are seen to be tangled masses of hyphae. Although alkaline digestion makes a specimen unsuitable for culture, sometimes treatment with sodium or potassium hydroxide and centrifugation makes it possible to find clumps of spherules in unstained specimens. A large volume may be *digested and centrifuged* as described above, or a drop or two may be mixed with sodium hydroxide on a slide

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*Millipore Filter Corporation, Watertown 72, Massachusetts.

Direct microscopic observation is also made possible by microculture, a rapid method for diagnostic study of mycelial growth. A drop of purulent material is mixed on a slide with a drop of saline and topped with a cover slip which is rimmed with vaseline. Examination during the next 24 or 48 hours will show the sprouting hyphae of *Coccidioides immitis* which can be traced back to the parent spherule or endospore. In one refinement of this method a few drops of Sabouraud's agar may be poured on a slide, allowed to solidify, inoculated with a loopful of material and covered as above.[113] In another modification germination of spores can be followed in hanging drops in Van Tieghem cells containing a liquid medium.[91]

Spherules can be made to stand out more clearly by adding equal parts of saturated solutions of iodine and Sudan IV.[91] Spherule walls become gradually darker as iodine is absorbed, and Sudan IV helps differentiate fat globules from them. Lactophenol cotton blue may also be used as for *arthrospores*.

## Culture Methods

***Glassware and Containers.*** Most of the historic studies of the morphology of *Coccidioides immitis* have been done in Petri dishes in which colonial characteristics are so beautifully demonstrated. The Petri dish is still unequalled for research purposes when morphologic definition is critical. Many laboratories have long used Petri dishes for routine clinical work without incident. However, because of the ease with which Petri dishes may be broken, some investigators warn against their use and suggest the substitution of test tube slants or the even less fragile medicine bottle or screw cap jar. A test tube need not be opened after mycelial growth has begun if a needle is thrust through or by the cotton plug in order to introduce materials or remove mycelial suspensions.[107] Rubber stoppers, rubber diaphragms through which needles may penetrate, and screw caps are frequently used with success, but Hampson has shown that variation in colonial morphology often results from tight closure of bottles or test tubes.[18]

***Culture Media.*** Because *Coccidioides* grows so easily on almost anything, scores of artificial media have been described for use in its culture, each purported to have a particular excellence. Because various media have been constructed to fulfill different purposes, they cannot be compared willy-nilly. One medium may optimally fill all the biochemical requirements of *Coccidioides immitis*, thereby giving luxuriant growth while allowing many other organisms to flourish as well. Another medium may support *Coccidioides immitis* parsimoniously but may support other fungi not at all, having the advantage of selectivity. Other media may promote safety of handling, although in them morphology is less characteristic

Another may have the advantage of easy availability in laboratories anywhere. Still others may fulfill peculiar experimental aims—such as the propagation of the spherule phase in vitro. Several media answering different needs will therefore be described: (1) standard laboratory media readily available everywhere; (2) media designed to promote optimal growth of *Coccidioides* and to provide standard conditions for mycologic study; (3) selective media for isolation of *Coccidioides* from contaminated materials; (4) liquid media for safe propagation of *Coccidioides*; and (5) specialized media for experimental investigation.

(1) *Standard laboratory media*

(a) Sabouraud's Dextrose Agar, easily available everywhere, is a good medium for *Coccidioides*, but it also supports many other organisms. The standard preparation contains 4 per cent dextrose. Roessler found that it is improved by reducing the dextrose to 1 per cent and raising the pH to 7.2.[417]

(b) Beef infusion glucose agar, blood agar, potato agar and other routine media are also usable. Friedman and Pappagianis have noted that in media containing peptone *Coccidioides* grows well but sporulates poorly.[96]

(2) *Media designed to promote optimal growth of* Coccidioides immitis *and to provide standard conditions for its study*. Stewart and Meyer have proposed that media should be chemically defined, so that morphological and physiological characteristics may be referred to an environment that can be duplicated anywhere.[31] Brain heart infusion agar is a satisfactory medium promoting rapid colonial growth. Excellent spore preparations can be made on agar containing 2 per cent glucose and 0.5-1 per cent yeast extract (Difco).

(3) *Selective media for isolation of* Coccidioides immitis *from contaminated materials*

(a) Smith's selective medium supports *Coccidioides* scantily, but other bacteria and fungi of animal origin grow hardly at all.[38] *Other soil fungi* may grow as well as *Coccidioides*, however, so that it is not useful for isolating *Coccidioides* from soil.

1 per cent ammonium chloride
1 per cent sodium acetate
0.8 per cent tribasic potassium phosphate
2 per cent agar

Autoclave at 15 lbs. pressure for 10 minutes. Just before pouring into Petri dishes add 0.04 per cent cupric sulfate.

(b) The cycloheximide medium of Georg, Ajello and Gordon is one of the most useful media for routine use because it selectively isolates *Coccidioides immitis* from among almost all other bacteria and saprophytic

fungi[619] It contains penicillin and streptomycin to inhibit bacteria and cycloheximide (Actidione®) to inhibit other fungi Even high concentrations of cycloheximide retard the growth of *Coccidioides immitis* and some other pathogens only slightly whereas saprophytic fungi are thereby almost completely inhibited

> Sabouraud s dextrose agar q s
> Penicillin 20 units per ml
> Streptomycin 40 units per ml
> Cycloheximide 0 1 mg per ml (For heavily contaminated material 0 5 mg per ml or 1 0 mg per ml may be used)

(4) *Liquid media for safe propagation of* Coccidioides Although the characteristic colony of *Coccidioides immitis* is obtained only on solid media their advantage is considerably lessened by the danger of handling cultures containing the highly infectious aerial mycelia Liquid media propagate the fungus in a form which can be safely handled and can be injected into animals for spherule identification

After trying more than 200 different combinations of synthetic materials Roessler and his co workers[41] proposed the following as a superior medium KHPO 0 15 M KHPO 0 015 M MgSO 0 008 M NHCHO 0 08 M glucose 2 per cent For a natural medium they proposed peptone 1 per cent glucose 2 per cent MgSO 0 008 M KHPO 0 015 M KHPO 0 015 M zinc 2 ppm plasmolized yeast 0 1 per cent

(5) *Specialized media for experimental investigation* Because so many substances have been tried for various purposes this type of media will be illustrated only briefly

A number of methods have been proposed for the production of spherules from mycelia in vitro one of the best being that of Lubarsky and Plunkett[804] In their medium they observed profuse growth of spherules without germination or mycelial production

| | |
|---|---|
| Sterile Tyrode s solution | 4 parts |
| Sterile rooster serum (from a 7 9 lb young cockerel) | 2 parts |
| Chick embryo extract (9 day old embryos pulverized in a Waring blendor with addition of 0 2 cc Tyrode s solution per embryo) | 2 parts |
| Solution filtered through a Seitz filter CO–O (76 7 per cent to 23.3 per cent) bubbled through the mixture at intervals (0 4 L over a period of 1 hour at about 12 hour intervals after inoculation with mycelial elements of *Coccidioides immitis* ) | |

Other methods for propagating spherules in vitro have been described by MacNeal and Taylor[41] Lack [46] Baker and Mrak [91] Conant and Vogel[780] Burke[64] and Converse[8 9]

***Culture Identification*** Identification of mycelia may be accomplished by morphologic study of the hyphae and confirmed by animal inoculation In making mycelial suspensions care must be taken to prevent atmos

pheric dispersion of the spores. It is unwise to open the container to pour liquid on the colony. Saline may be injected through or past the cotton plug of an agar slant with a syringe needle through which the suspension may be withdrawn after the mycelial fragments are mixed.

For morphologic identification a drop of the mycelial suspension is mixed on a slide with a drop of lactophenol cotton blue and the preparation is studied microscopically for the barrel-shaped arthrospores and alternating empty cells of *Coccidioides*.

Lactophenol Cotton Blue Stain

| | |
|---|---|
| Phenol crystals | 20 Gm |
| Lactic acid | 20 cc |
| Glycerol | 40 cc |
| Distilled water | 20 cc |

Dissolve by heating gently under a hot water tap. Add 0.05 Gm cotton blue.

***Precautionary Measures.*** The danger of laboratory infections (see Chapter Five) must color any discussion of mycologic procedures applicable to *Coccidioides*. The only theoretically certain preventive measure would be for laboratories to refuse to deal with the fungus, thus depriving the clinician of important data. Unfortunately, even such a rigid practice may fail, for laboratory personnel may handle *Coccidioides* unawares.

Various measures have been taken to minimize the danger. After colleagues in distant parts of the same building had been infected, C. E. Smith ceased growing the fungus on solid media in his laboratory. It has even been suggested that *Coccidioides* be handled only by personnel known to be immune, and then only in isolated buildings barred to all others. In the laboratory of Looney and Stein it was forbidden that suspicious cultures be opened until autoclaved. Keeney of Johns Hopkins designed a stainless steel box with a plate glass top and armholes fitted with long sleeves of rubberized silk terminating in gloves.[44] Smith preferred a chamber similar to that described by Meyer for use with plague bacilli.[47] Bacteriologic hoods are often used, an added precaution being the exhaustion of the air through an incinerator.[91] Gowns, gloves and masks are required in some laboratories, although logic and experience prove gauze masks a feeble defense, for infections have been acquired despite their use.[34, 41] Petri dishes are generally proscribed for routine cultures of *Coccidioides*, although in laboratories where they are used with care and discretion they have not been an undue hazard.

In a laboratory where *Coccidioides* is constantly handled, my colleagues have successfully used the following method. A solid medium selectively promoting *Coccidioides* is inoculated and the culture is examined daily thereafter. As soon as a flat membranous colony is visible, a loopful of material is transferred to liquid media. At this stage, about two days

after inoculation the colony is still moist and yeasty the infectious aerial mycelium not yet having developed After transfer the original culture is immediately and permanently sealed with scotch tape but is observed long enough to allow identification of the colony before it is autoclaved

Such a method is advisable only when personnel are constantly alert to the danger If the colony is allowed to develop too long before the transfer is made infectious spores will of course be present It is not for the uninitiated A similar procedure has been described by Creitz and Puckett [791]

***Preparation of Cultures for Gross Demonstration*** When desired for gross demonstration cultures of *Coccidioides* should be inactivated or a non pathogenic simulant such as *Oospora* should be used Cultures may be killed without significantly altering their gross appearance by suspend ing them above 25 50 cc of concentrated formaldehyde in a closed con tainer for 24 hours at 37° C or for a week at room temperature [969] Des sicators or any other tightly closing jars may be used Petri dishes are in verted above the fluid The formaldehyde odor may be dissipated by leav ing the dead culture exposed to room atmosphere

## Animal Inoculation Methods

One cubic centimeter of the mycelial suspension or suspected spherule containing material is inoculated intraperitoneally into each of four mice or 0 1 cc intratesticularly into guinea pigs Tween 80 is sometimes added to the inoculate After 4 to 6 days spherules can be demonstrated in pus from the resulting orchitis or peritonitis In 10 to 14 days mice succumb with lesions of the lungs omentum spleen and at the point of inocula tion Histologic examination reveals the typical endosporulating spherules of *Coccidioides*

Refinements of inoculation procedures for quantitative studies of viru lence have been proposed by several investigators Strauss and Kligman found that rapidly and uniformly fatal coccidioidal infections were pro duced if suspensions of *Coccidioides* in dilute hog gastric mucin were injected into mice [674] Karrer noted that intracerebral inoculation of mice was more sensitive than intraperitoneal because the latter required such large doses of the fungus [7 6] Friedman and her co workers however dem onstrated that accurate determinations of virulence could be made by intraperitoneal injection if measured numbers of viable particles of *Coccidioides immitis* were used [8 1] Mycelia were broken and evenly dispersed in saline by mixing for six hours in a flask containing glass beads Counts were made by inoculating pour plates with the suspensions Stock saline suspensions stored at 4° C to inhibit germination were diluted to the

appropriate concentration of fungus particles. By this means doses of 100 viable particles could be injected when desired.

## Tissue Staining Methods

Although staining with hematoxylin and eosin will sometimes demonstrate *Coccidioides*, it often fails to provide the desired contrast between parasite and host tissues. The periodic acid Schiff technique in the Hotchkiss-McManus [9] or Gridley [74] modifications is superior (Fig. 13). Pathogenic fungi contain certain carbohydrates, mucoproteins and glycoproteins which are oxidized by periodic acid to aldehydes which in turn form colored compounds with the Schiff reagent.

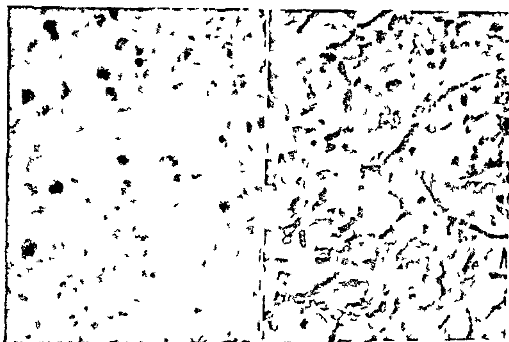


Figure 13. Sections of a chronic coccidioidal cavity of the lung. Left, stained with hematoxylin and eosin, showing little but caseation necrosis. Right, stained by the Hotchkiss-McManus technique with the same magnification, showing a heavy network of mycelium. (From Seabury, Peabody and Liberman: *Diseases of the Chest* 25 [illegible], January 1954.)

The more recently published Grocott silver stain [illegible] promises to excel even the periodic acid Schiff technique. The methenamine silver nitrate procedure originally designed by Gomori as a histochemical test for glycogen and mucin was adapted by Grocott for mycologic study. Although intended primarily for photomicrography, it has already become the standard procedure in some mycologic laboratories [illegible]. Its advantages over

the Hotchkiss McManus and Gridley stains are its simplicity and dependability its sharp black and white delineation and its use of more stable solutions Spherules and endospores of *Coccidioides* stand out sharply in black (Fig 14) Individual endospores are sometimes found when other stains give negative results

A simple technique using Parker 51 Fountain Pen Ink has been described by Sorensen Fiese and Chen[96] Although less precise than the periodic acid Schiff or Grocott techniques it has often demonstrated *Coccidioides* when routine staining methods have failed

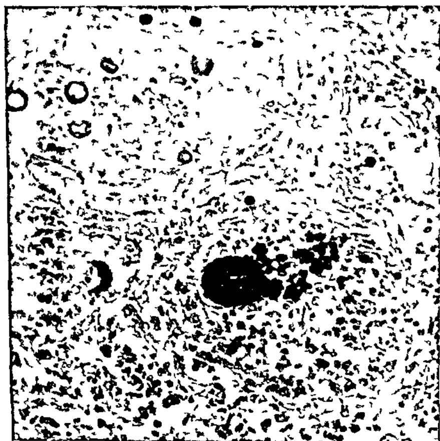


Figure 14 Spherule of *Coccidioides immitis* human lung Grocott silver stain (Gomori s methenamine silver technique) (Reproduced by permission from Grocott *American Journal of Clinical Pathology* 25 975 979 1955 )

*Hotchkiss McManus Stain (periodic acid Schiff technique)*

1 Fix tissues in any routine fixative
2 Process embed in paraffin and section

3 Deparaffinize in xylol
4 Immerse in absolute alcohol
5 Rinse in distilled water
6 Immerse two slides simultaneously in 1 per cent periodic acid fo[r] 10 minutes
7 Rinse in tap water
8 Immerse for 2 minutes in this solution

| | |
|---|---|
| Basic fuchsin | 0 1 Gm |
| 95 per cent alcohol | 5 ml |
| Water | 95 ml |

9 Wash in tap water
10 Immerse one slide for 10 minutes and the other for 30 minutes in this solution

| | |
|---|---|
| Zinc hydrosulfite | 1 0 Gm |
| Tartaric acid | 0 5 Gm |
| Water | 100 ml |

11 Wash in tap water for one minute
12 Counterstain with light green or with saturated aqueous solution of picric acid for two minutes
13 Rinse in tap water
14 Dehydrate clear and mount

In sections thus prepared walls of spherules and endospores stain brilliant red

*Gridley s Stain (periodic acid Schiff and Gomori's aldehyde fuchsin stain)*

1 Fix tissues in any routine fixative
2 Process embed in paraffin and section at 6 micra
3 Affix to slides with Mayer s egg albumin and dry
4 Deparaffinize to distilled water
5 Immerse in 4 per cent chromic acid for an hour
6 Rinse in running tap water for 5 minutes
7 Immerse in Coleman s preparation of Feulgen reagent for 15 minutes

| | |
|---|---|
| Basic fuchsin | 1 Gm |
| *Boiling water* | 200 *ml* |
| Dissolve filter cool | |
| Potassium metabisulfite | 2 Gm |
| 1 N hydrochloric acid | 10 ml |
| Let bleach for 24 hours | |
| Activated carbon | 0 5 Gm |
| Shake for 1 minute filter through coarse paper | |

8 Rinse 3 times in sulfurous acid rinse 2 minutes each

| | |
|---|---|
| 10 per cent sodium metabisulfite | 6 ml |
| 1 N hydrochloric acid | 5 ml |
| Distilled water | 100 ml |

9 Wash in running tap water for 15 minutes
10 Immerse in aldehyde fuchsin solution for 15 minutes

| | |
|---|---|
| Basic fuchsin | 1 Gm |
| 70 per cent ethyl alcohol | 200 mL |
| Paraldehyde | 2 ml |
| Hydrochloric acid | 2 ml |
| Keep in refrigerator for 3 days until deep blue | |

11 Rinse off excess stain in 95 per cent alcohol
12 Wash well in water
13 Counterstain in metanil yellow solution for 2 to 5 minutes

| | |
|---|---|
| Metanil yellow | 0 25 Gm |
| Distilled water | 100 ml |
| Glacial acetic acid | 0 25 ml |

14 Wash in water
15 Dehydrate clear and mount

With this technique spores and hyphae are both well stained Hyphae stain deep blue and spherules deep rose or purple against a bright yellow background

*Grocott Silver Stain (Gomori's methenamine silver technique "GMS stain")* [a, j]

*Solutions*

1 Five per cent aqueous chromic acid (chromium trioxide $CrO_3$)
2 Stock methenamine silver nitrate solution Add 5 ml of 5 per cent $AgNO_3$ to 100 ml of 3 per cent methenamine U S P grade $(CH_2)_6N_4$ A white precipitate forms but immediately dissolves on shaking The clear solution remains usable for months at refrigerator temperature
3 One per cent aqueous sodium bisulfite ($NaHSO_3$)
4 Five per cent aqueous borax U S P grade ($Na_2B_4O_7 \cdot 10H_2O$)
5 One tenth per cent aqueous gold chloride ($AuCl_3 \cdot HCl \cdot 3H_2O$) This may be used repeatedly
6 Two per cent aqueous sodium thiosulfate ($Na_2S_2O_3 \cdot 5H_2O$)

*Procedure*

1 Deparaffinize sections in xylol and run through alcohols to water Smears are prepared on albumin treated slides and fixed in 95 per cent

alcohol Slides previously stained with hematoxylin and eosin may be used by removing cover glasses in xylol and running through alcohols to water Subsequent chromic acid treatment will remove any remaining stain

2 Hydrated sections and smears are oxidized in 5 per cent chromic acid for 1 hour washed in running water 10 minutes and then treated in sodium bisulfite for 1 minute to remove any residual chromic acid They are then washed in tap water for 5 minutes and finally in 3 changes of distilled water

3 Silver at 45 50°C in a working solution prepared by adding 25 ml of stock methenamine silver nitrate to an equal portion of distilled water containing 1 to 2 ml of 5 per cent borax Fungi and mucin will begin to stain yellowish brown in 25 to 30 minutes and will be adequately stained at the end of 1 hour Slides are then rinsed in distilled water 2 or 3 times

4 Tone in 0 1 per cent gold chloride for 5 minutes This will also bleach the background Rinse in distilled water

5 Remove unreduced silver by treating with 2 per cent sodium thiosulfate for 1 or 2 minutes and after washing thoroughly counterstain if desired Aqueous safranin may be used if a red nuclear stain is desired or a light hematoxylin eosin combination may be used if tissue detail is important

6 Dehydrate clear and mount as usual

*Results*

Fungi are sharply delineated in black with the inner parts of mycelia and hyphae staining an old rose as a result of toning in gold Mucin also assumes a rose red color as a result of toning

*Chapter Four*

# Geographic Distribution of *Coccidioides immitis*

- Methods of Geographic Study
- North America
  - California
  - Arizona
  - New Mexico
  - Texas
  - Nevada and Utah
  - Other States
  - Mexico
- Central America
- South America
  - Argentina
  - Paraguay
  - Bolivia
  - Venezuela
  - Uruguay
  - Chile
  - Brazil
  - Ecuador
- Europe
- Africa
- Asia
- Other Parts of the World

The first two reported cases of coccidioidomycosis roughly indicated the main areas of endemicity of *Coccidioides immitis*—the Gran Chaco Pampa region of South America and the southwestern United States The boundaries of the endemic zones have been more precisely delimited but with only two or three exceptions no new areas have been discovered Except for Venezuela Central America and Mexico endemicity has not yet been proven elsewhere Sporadic infections in other parts of the world appear to be "imported" or due to transport of the fungus by fomites

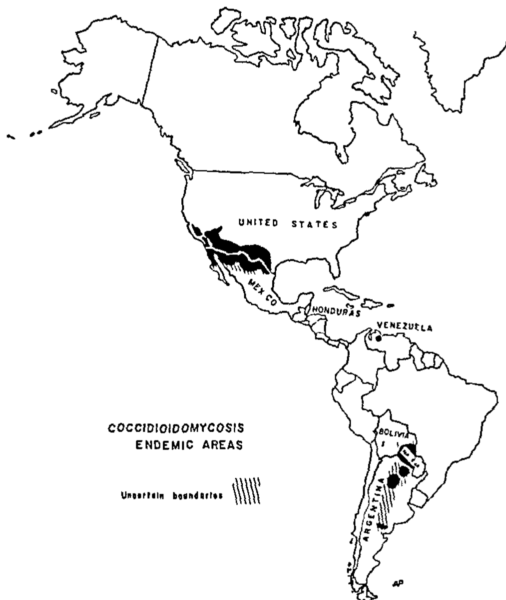



Figure 15. Map showing approximate boundaries of areas where *Coccidioides immitis* is known to exist in North, Central and South America.

## METHODS OF GEOGRAPHIC STUDY

There are several ways by which the presence of *Coccidioides immitis* may be demonstrated.

(1) ***Isolation of the Fungus from the Soil.*** From the theoretic standpoint this method would appear to be most valid. It was successful on three historic occasions (Stewart and Meyer, 1932;[15] Davis, Smith, and

Smith 1942[319] and Emmons 1942[373]) and has recently been adapted to experimental ecologic study by Egeberg Ely Lubirsky Plunkett and others It is currently yielding much worthwhile information especially in uninhabited areas

(2) *Identification of* Coccidioides immitis *in Wild Animals* In defining the endemicity of a given area this method is almost as conclusive as the first It was first employed by Emmons who demonstrated the fungus in various species of wild rodents in the southwestern states[3, 3, 3, 4]

(3) *Identification of* Coccidioides immitis *in Domestic Animals* This method is less conclusive than demonstration of the fungus in wild animals for two obvious reasons (a) stock animals and pets may be transported from one area to another and (b) they are exposed to fomites at least as often as their human masters Straw used for bedding hay and even the dust on other animals have been implicated in cases of animal coccidioidomycosis in non endemic areas Nevertheless because of constant governmental inspection of carcasses in abattoirs coccidioidal lesions have been found in sufficient numbers to be statistically significant

(4) *Morbidity Reports of Human Coccidioidomycosis* These were the earliest clues to the distribution of the fungus and are still a most important source of information Early reports concerned only the secondary form of the disease—as indeed they still do except in the southwestern states of this country In other states and countries reports with few exceptions still concern coccidioidal granuloma or residual pulmonary lesions In southwestern states reports of primary coccidioidomycosis are *more important in localizing endemicity than reports of secondary forms* Primary coccidioidomycosis is closely related chronologically to exposure whereas coccidioidal granuloma may be diagnosed so long afterward that the site of exposure can be inferred only in retrospect

(5) *Coccidioidin Skin Testing Survey* Mass population survey by this means is a most useful epidemiologic method First applied in California it has now been used in many other states as well as in Europe Central America and South America School children college students hospital patients and groups of employees have been most often studied Possible sources of error which have to be evaluated are (a) cross reactions with other antigens known and unknown and (b) previous travel or residence in other endemic areas

(6) *Skin Testing Home Grown Domestic Animals* Maddy[949] has developed one of the most precise of all methods by skin testing home grown cattle i e cattle who have never been *taken more than a few* hundred feet from the spot where they were born Already he has applied

it extensively in Arizona and some of the adjacent areas It promises to define not only endemic areas in general but also small "pockets" of high infestation within general areas

## NORTH AMERICA

The North American habitat of *Coccidioides immitis* involves parts of the American states of California Arizona Nevada Utah New Mexico and Texas, and the Mexican states of Baja California Sonora Chihuahua and Coahuila The area is roughly co terminous with the Lower Sonoran Life Zone the eastern half of which includes Coahuila Chihuahua and arid west Texas whence its Rio Grande and Pecos Valleys reach northward into New Mexico The zone is interrupted by the continental divide to begin again in Arizona and Sonora spreading over the deserts of southern Nevada southeastern California Baja California and the San Joaquin Valley One narrow arm follows the Grand Canyon of the Colorado into northern Arizona and another follows the Virgin River into southwestern Utah around St George

### California

In the earliest North American paper on coccidioidal disease Rixford correctly surmised that the San Joaquin Valley was somehow associated with the infection although he had then seen only two cases Speaking before the California Academy of Medicine in 1894 he said

> Dr Thorne's patient was a native of the Azores Islands but had resided here 14 years My patient was also a native of the Azores and had lived here seven years Both were previously healthy and worked in the San Joaquin Valley for some time before the trouble began My patient had also worked about the docks in Port Costa and San Francisco in unloading ships many of which came from the tropics It was thought possible that the infection was acquired in the hold of one of these vessels However since two cases have occurred here both hailing from the San Joaquin Valley it may be that the origin of the infection is nearer home

Eleven years later Ophuls opened his address before a section of the American Medical Association with these words "We have in California a peculiar form of oidiomycosis of which so far no cases have been described in people who have not been in our state except the very first case in Buenos Ayres"

Before long the geographical association was so well recognized that coccidioidal granuloma was often called the "California Disease" On one occasion an editorial storm erupted in Bakersfield when someone pinpointed the disease even further by calling it the "San Joaquin Valley

disease Dr Joe Smith of Kern County recalled that on this occasion the editor of *The Bakersfield Californian* harshly criticized the State Board of Health for this "infamous advertising of our fair valley"[41]

At the present time the areas where *Coccidioides* exists are fairly accurately known although question still remains concerning certain borderline cities and towns In brief outline the area includes the San Joaquin Valley decreasing from south to north the neighboring counties across the mountains to the west and south and the desert counties bordering on Arizona and Mexico In all some 17 of the 58 counties in the state have been implicated

*San Joaquin Valley* The vast Central Valley of California is one of the most fertile areas in all the world A great longitudinal trough about 450 miles long and 50 miles wide it contains two thirds of California s farm lands The nearby Pacific Ocean and the protecting mountains low on the west and towering on the east give the valley a uniform climate with hot summers mild winters and a low average annual rainfall confined almost entirely to the winter months The level floor is formed of a great many alluvial fans laid down by streams and rivers originating in the high Sierras and other ranges of mountains Under the alluvial plain is a thick sedimentary blanket source of prolific oil deposits a remnant of geologic ages when the sea covered the valley The Sacramento River draining the northern half and the San Joaquin River draining much of the southern half unite to enter the San Francisco Bay South of the San Joaquin watershed proper although still in the San Joaquin Valley there is a system of interior drainage where the Kings and Kern Rivers enter Tulare and Buena Vista Lakes

Not many generations ago the San Joaquin Valley was but a desert through which great rivers flowed unused Diversion of the waters into complex irrigation systems has transformed the desert into one of the richest agricultural areas of the United States producing cotton grapes wine figs peaches citrus fruits and many other crops

The southern and western part of the valley has long been an important source of petroleum and natural gas On the eastern side in the lap of the Sierras is the Orange Belt" rich with citrus fruit The valley floor supports the fruit cotton and grapes which have made it so wealthy All or parts of eight counties form the valley proper—Kern Tulare Kings Fresno Madera Merced Stanislaus and San Joaquin

The endemicity of coccidioidomycosis is highest in the south and tapers off toward the northern part of the San Joaquin Valley Kern County is most highly endemic followed by Tulare Kings and Fresno counties North of Fresno endemicity is spotty on the east side of the

valley, but on the west it continues as far north as Tracy in San Joaquin County. On the west and south it spills across the Coast Range into San Benito, Monterey, San Luis Obispo, Santa Barbara, Ventura and Los Angeles Counties.

***Kern County.*** Kern County is the area *par excellence* for the study of coccidioidomycosis. It was there that the relationship between Valley Fever and coccidioidal granuloma was worked out. More clinical studies of the disease have come from the practicing physicians in Bakersfield than from any other similar group. Observations long taken for granted in Kern County provoke great interest elsewhere. As Helen Mackler put it: "World War II brought a swarm of case reports from the multitude of medical people transplanted from research centers to unhappy localization in desert training camps. Those of us who live in an area where a case experience of 500 patients is not too unusual may smile at the excitement which invests some of these individual cases."[illegible]

Kern County is the site of conjunction of the three mountain ranges which enclose the Great Valley *on the south—the Temblor or Coast Range* on the west, the Tehachapi mountains to the south, and the lower reaches of the Sierra Nevada on the east. Rich oil fields underlie the western and *southern parts of the county, and the valley floor, although hot and arid,* is extremely fertile.

All of that part of Kern County which lies within the San Joaquin *Valley is highly endemic. From the west side oil towns around Taft came* many of the early cases of Valley Fever. The agricultural townships of Arvin, Shafter, Wasco and Delano, with a third of the population of the county, *were the source of two thirds of the early cases of disseminated coc*cidiodomycosis.[illegible] Studies at Minter and Gardner Air Fields during World War II showed the speed with which large groups of non-immune *men become infected.*

Coccidioidin surveys by Myrnie Gifford, C. E. Smith, Juliet Thorner and others have showed the high incidence of positive reactions among *permanent residents of Kern County.*[illegible, 3, 4] *In some studies* 90 per cent of long-time residents have reacted positively to coccidioidin skin tests. Thorner showed that the incidence of reactions among children was directly *proportional to the length of time* that they had been in Kern County. In her series the percentage of positive reactors varied from 25 per cent in those who had been in the county less than a year to 76 per cent *in those who had been there 10 years or more.*[illegible]

The habitat of *Coccidioides immitis* in Kern County overflows the area within the San Joaquin Valley, extending eastward across the Te*hachapi mountains into the Mojave Desert.* During World War II it was found that an appreciable number of men, about 6 per cent, con

tracted either frank or inapparent infections within four or five months after their arrival at Mojave California[41] Plunkett has demonstrated a focus of *Coccidioides immitis* near Inyokern fifty miles northeast of Mojave adding further confirmation to the concept of patchy endemicity throughout the vast reaches of the southeastern deserts of California[84]

*Tulare County* Tulare County is situated in the eastern part of the San Joaquin Valley and the mountains of the Sierra Nevada Continuous on the south with Kern County its southern agricultural areas are highly endemic for coccidioidomycosis and its northern reaches are only little less so It was in Kern and Tulare Counties that the classic epidemiologic studies of Smith were carried out[73] The cities of Porterville Farmersville Lindsay and Exeter are surrounded by endemic regions and Visalia Tulare and Dinuba also have their share of cases

Wm A Winn of Springville Tulare County has made outstanding contributions to the clinical understanding of coccidioidomycosis including the definitive description of the residual coccidioidal cavity It was as Medical Director of the Tulare Kings County Tuberculosis Hospital at Springville that he made his observations[63] Probably no one has so carefully studied more cases of pulmonary coccidioidomycosis

*Kings County* Kings County is located exclusively in the western half of the San Joaquin Valley between Kern and Fresno Counties so that the whole county is within the endemic area During World War II an excellent opportunity was realized to compare it with Kern County in that Lemoore Air Base near Hanford was one of the four air fields studied by C E Smith and his associates[4] It was found that the infection rate rose and fell in the same general pattern that prevailed at Minter and Gardner Fields in Kern County but at a lower level The incidence at Lemoore was about half that at the southern fields

*Fresno County* In general the incidence of coccidioidomycosis in Fresno County is only about a quarter that of Kern County but except for the mountainous areas in the east no part of the county is known to be entirely free Fresno City itself is not so highly endemic as some other parts of the Valley but the fungus abounds not far away particularly to the south and west In recent years many large ranches some of them comprising several thousand acres have been established on the west side of Fresno County attracting large aggregations of non immune farm workers often transient to the cotton fields cotton processing plants and melon fields In this highly endemic area are Coalinga and its oil fields and the agricultural towns of Firebaugh Mendota Tranquillity San Joaquin Cantua Creek Five Points and Huron

The farm lands in the middle of the county surrounding the cities along U S Highway 99 are less heavily infested but numerous infec

tions originate even up to the eastern foothills. Several of my patients apparently contracted the disease at Pine Flat Dam on the Kings River, well into the foothills of the Sierra Nevada.

*Madera County.* The relatively small part of Madera County to the west of U. S. Highway 99 is endemic but in general the concentration of the fungus is noticeably less than in the more southerly counties. Chowchilla on U. S. Highway 99 is about the northernmost point where endemicity reaches as far east as the middle of the Valley.

*Merced County.* In Merced County endemicity is fairly well limited to the western strip of the county, in and near the foothills of the Coast Range. Infections originate around Los Banos and Gustine but less often further east.

The precise studies done in the San Joaquin Valley Air Fields during World War II showed the striking contrast between Castle Field near Merced and Minter and Gardner Fields near Bakersfield.[4] In 1943-1944, for instance, the infection rate per 100 susceptible men at Minter Field was 15.61; at Merced it was 0.36. Some of those infected while stationed at Merced had actually travelled in the southern part of the Valley within the period of incubation.

*Stanislaus County.* There is very little coccidioidomycosis at Modesto in the middle of the Valley or to the east. Along the western hills there is patchy endemicity.

In 1945 Cheney and Denenholz reported the results of coccidioidin skin testing surveys among officer personnel at Hammond General Hospital in Modesto.[3] During a year of observation skin tests changed from negative to positive in only 10 of 360 individuals or 2.8 per cent. Although these men were resident in Modesto throughout the period they probably travelled into known endemic areas only a few miles away.

*San Joaquin County.* The southwestern corner of San Joaquin County marks California's northernmost known habitat of *Coccidioides immitis*. Endemicity extends through Vernalis almost to Tracy.

*San Benito County.* San Benito County is comprised in large part of the low mountains forming part of the Diablo or Coast Range. The arid Panoche Pass between the San Joaquin and San Benito Valleys was the site of the "rattlesnake hole" epidemic mentioned in Chapter Two where *Coccidioides immitis* was isolated from the soil.[40] Cases of coccidioidomycosis are seen now and then in Hollister.

*Monterey County.* The southeastern corner of Monterey County was found to be endemic in 1942 when several cases of acute coccidioidomycosis occurred in Army personnel stationed at Camp Roberts, a large mili

tary reservation on the western slopes of the Coast Range in Monterey and San Luis Obispo Counties [34] Endemicity was demonstrated to be patchy for the disease was prone to appear in some companies and to spare others although bivouacs were not far apart

***San Luis Obispo County*** San Luis Obispo County is separated from Kern County only by the low mountains of the Coast Range Northern San Luis Obispo County has areas of endemicity around Camp Roberts San Miguel and Paso Robles and eastward to the hills The city of San Luis Obispo itself is not endemic

One of the well known military epidemics occurred among personnel of Camp San Luis Obispo after dusty maneuvers with mechanized infantry equipment Goldstein and Louie[11, 141] reported the clinical findings and Colburn[38] reported the roentgenologic findings in 75 cases of acute coccidioidomycosis

***Santa Barbara County*** Scattered cases of coccidioidal infection have been reported from Santa Barbara County one in a Filipino farm laborer who had been in Lompoc for 15 years [131] According to Smith endemicity does not reach the coast [6]

***Ventura County*** At least the southeastern quarter of Ventura County is endemic and probably also other areas Several cases have been reported from Santa Susana Moorpark and Fillmore It is not surprising that these little coastal valleys and their dry hills harbor the fungus Simi Valley is separated from the known endemic area of Chatsworth and Canoga Park by only four miles Endemicity appears not to extend to the coast where ocean fogs are unfriendly to *Coccidioides*

***Los Angeles County*** It has been known for many years that some of the patients with coccidioidal granuloma at the Los Angeles County Hospital had never been in the San Joaquin Valley In the past few years studies of epidemics in detention camps in several locations have nicely demonstrated the endemicity of coccidioidomycosis in the San Fernando Valley In a Forestry Camp near Saugus several apparent and other inapparent infections occurred in personnel who were known to have been detained in the camp during the incubation period [7] A similar epidemic occurred among boys resident in a facility near Chatsworth at the western edge of the San Fernando Valley [37] Coccidioidin skin tests done in high schools have showed an increasing incidence as one goes northward from downtown Los Angeles into the San Fernando Valley [9] In Los Angeles the incidence was 1 6 per cent at Newhall 5 per cent and at Canoga Park near Chatsworth 13 per cent

***San Bernardino County*** A number of cases of coccidioidomycosis have been seen in San Bernardino Colton Barstow and Needles although

only part of the sparsely settled desert has been studied. It is likely that a considerable section of this large county harbors the fungus. Part of of it is included in the desert area studied by Willett and Weiss.[20]

***Riverside County.*** An epidemic occurring among army personnel afforded Forrest M. Willett and his colleagues an opportunity to delineate roughly an area of endemicity in the southeastern corner of California, a great irregular triangle bounded by Banning, Needles, and Yuma.[20] Banning, near the edge of the desert, was endemic; March Field, near Riverside a few miles away, was not. The clinical study of Willett and Weiss concerning 83 hospitalized patients was one of the outstanding contributions to the knowledge of the disease as it occurred in military installations.

Another small epidemic reported by Goldstein and McDonald established the endemicity of coccidioidomycosis in barren mountains of eastern Riverside County.[161] Ten cases of primary coccidioidomycosis occurred among military personnel who had been at Pallen Pass not far from the California-Arizona border.

A coccidioidin survey of high school students in Banning and Palm Springs showed a 17 per cent incidence of positive reactions, the highest found by Kessel and his co-workers in Southern California.[illegible]

***Imperial County.*** Imperial Valley, with its desert, dry hills, and artificially irrigated farm lands, would seem to be a likely habitat for *Coccidioides immitis*, but knowledge concerning the area is incomplete. There is patchy endemicity in Imperial County, and it is in the general area implicated by Willett and Weiss,[illegible] but the exact locations of the hazard are an enigma. Mexicali, just across the border in Mexico, was the site of the 1950 coccidioidin survey of Drs. Slim Villegas and Aranda Reyes,[61] in which an incidence of 33 per cent positive reactions was found.

***San Diego County.*** The exact sites where the fungus lives in San Diego County are unknown, but there are suggestions that part of the rural areas are endemic. The best known case in San Diego was that of the gorilla in the zoo.[31] The huge animal died of acute disseminated coccidioidomycosis after an illness of a month and a half. It is presumed that he inhaled the spores of *Coccidioides* when he and his cage mate tossed over themselves the dusty bedding straw which had been brought in from rural San Diego County. Other cases, possibly indigenous, have occurred in San Diego County.

***Northern California.*** Occasional cases of coccidioidal granuloma have been reported from near Woodland in Yolo County, from Contra Costa County, and from other areas of northern California, but true endemicity has not been demonstrated there. Handling of products from the San

Joaquin Valley or trips to endemic areas have usually been suspected The Sacramento Valley is apparently free of the disease

## Arizona

Although suspected for years the endemicity of coccidioidomycosis in Arizona was not demonstrated until after the work of Gifford and Dickson in California Farness recalls that he stumbled on the first case" in 1937 because of his interest in moniliasis [91] In 1938 Woolley found *Coccidioides immitis* in the sputum of patients being erroneously treated for tuberculosis in Arizona In 1939 Storts reported a case of coccidioidal meningitis in a four year old child native to Tucson [7] In the same year Brown demonstrated positive coccidioidin reactions in patients with erythema nodosum ' and Phillips found a number of positive reactors among residents of Phoenix [5] In 1940 Farness and Mills described a series of cases of coccidioidal disease in southern Arizona [98] In 1942 Aronson Saylor and Parr[3, 19] revealed the unexpectedly high incidence of positive coccidioidin reactions among Indian children on several Arizona reservations (Sells Papago agency 94 2 per cent San Carlos agency 93 per cent Pima agency 83 6 per cent and Fort Apache agency 14 9 per cent) An incidence of over 90 per cent is higher than that obtained in any other similar group of children In 1942 and 1943 Emmons reported the isolation of *Coccidioides immitis* from the soil and from several species of rodents trapped near San Carlos Tucson Casa Grande and Phoenix [247] The implication of this series of studies is that southern Arizona has the highest endemicity of any area yet studied Both Phoenix and Tucson are in the highly endemic area At Phoenix 42 per cent of the school children between 5 and 17 reacted positively to coccidioidin in a series reported by Emmett [69] At Florence southeast of Phoenix 50 per cent of susceptibles are infected within only six months [6] Most of the cases come from the two counties of Maricopa (Phoenix) and Pima (Tucson) (Table IV) Northern Arizona is probably not an endemic area except in the northwestern corner and along the Colorado River

## New Mexico

The first case of coccidioidal granuloma known to have originated in New Mexico was reported in 1927 by Riesman and Ahlfeldt [84] There is an irregular band of endemicity across the southern part of the state continuous with endemic areas in Texas Arizona and Mexico The limits of the involved area though not precisely known can be inferred from the outlines of the Lower Sonoran Life Zone (Fig 16) Northern New Mexico including the cities of Albuquerque and Santa Fe is spared [6]



Figure 16 The Lower Sonoran Life Zone in the southwestern United States roughly coterminous with the natural habitat of *Coccidioides immitis* (Courtesy Dr Keith T Maddy)

## Texas

In 1913 a young Texas physician died of a rapidly fatal mycosis[3] When MacNeal and Hjelm identified the causative parasite as *Coccidioides immitis* they supplied the first clue to a new endemic area larger even than that of California[3] Yet when Caldwell in 1932 reported three new cases of coccidioidal disease he could cite only two previously recognized in Texas[140] In 1933 L M Smith described a case originating in west Texas[17] In 1935 Lehman and Pipkin reported a case from San Antonio[illegible]

In 1942 several new studies were completed in Dallas by Caldwell[20] in El Paso by L M Smith[33] and in San Angelo by Schulze [illegible] Caldwell observed that if the ratio of acute cases to chronic cases is several hundred to one then an appalling number of them are being overlooked Schulze recognized 4 cases of primary coccidioidomycosis originating in San Angelo in 3 years time and reported an 18 per cent incidence of coccidioidin reactors among west Texas residents In 1946 Haynes reported a 2.66 per

cent incidence in Dallas which city is itself northeast of the endemic zone [40]

C I Smith states that the entire Rio Grande Valley west of Mission Texas is involved [6] There is patchy endemicity around San Antonio but the area does not extend as far north as Wichita Falls Houston Fort Worth and Dallas are outside it Further west San Angelo and El Paso are in the involved region El Paso s incidence of infection is comparable to that of Phoenix Arizona and Bakersfield California

In 1953 1954 several Air Force Bases in the southwestern states co operated in a study of the incidence of coccidioidomycosis among their personnel [83] Three of the Texas bases form a curved line near the eastern extremity of the endemic area (1) Webb AFB Big Spring Texas (2) Goodfellow AFB San Angelo Texas and (3) Laredo AFB Laredo Texas The incidence of coccidioidin conversions per 1 000 susceptibles per year at these three bases was only 25 8 23 5 and 43 respectively compared to 310 at Williams AFB in Chandler Arizona an area of high endemicity These findings demonstrate the tapering off of endemicity in central Texas

An imaginary line running more or less north and south separates Texas into two different climates and life zones the Lower Sonoran to the

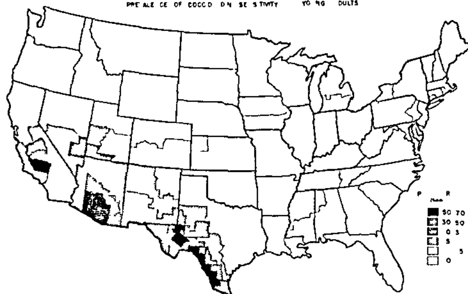


Figure 17 Geographic distribution of frequency of coccidioidin reactors among 48 676 young adults *Coccidioides immitis* is known to exist in areas of high incidence A low incidence of positive reactions occurs in areas where histoplasmosis is endemic (From Edwards and Palmer *Diseases of the Chest* 31 35 60 January 1957 )

west and its Lower Austral counterpart to the east.[93] In the latter zone rain occurs on and off throughout the year and averages 40 inches or more. To the west, rain is more restricted to winter months and averages only 10 to 16 inches per year. To the east, vegetation is more dense; to the west, vegetation is more sparse, winds are stronger, and dust is more prevalent. Malaria exists to the east but not to the west of the line. The incidence of reactions to histoplasmin increases toward the east and of reactions to coccidioidin toward the west.

## Nevada and Utah

An arm of the Lower Sonoran Life Zone extends along the Colorado River into northwestern Arizona and southern Nevada and follows the Virgin River into southwestern Utah. Coccidioidomycosis is mildly endemic in this area around Las Vegas, Nevada, and St. George, Utah, as demonstrated by skin testing surveys and the finding of *Coccidioides* in rodents.[67]

## Other States

Cases of disseminated coccidioidomycosis and residual pulmonary lesions have been seen in all parts of the United States, so that the question of widespread endemicity has been raised periodically for 50 years. An analysis of such cases shows that most patients have previously been in one of the endemic areas of the southwestern states. A few have not, but in their cases the possibility of fomite transmission is strong. With modern epidemiologic techniques it has been possible to delimit the areas of endemicity to those mentioned above. Although it is to be expected that knowledge within the southwestern states will become more precise, it is unlikely that any new indigenous areas will be found elsewhere in the United States.

## Mexico

Coccidioidomycosis has always been of relative importance to Mexicans living in the United States because of their moderately increased susceptibility to dissemination. Studies of endemicity of *Coccidioides* have recently been undertaken in Mexico itself, those of Dr. Antonio González Ochoa of the Institute of Health and Tropical Diseases in Mexico City being most extensive.

The first Mexican studies of coccidioidomycosis, which concerned a case imported from California, were those of Cicero[44] and Perrin in 1932. González Ochoa's work followed a visit he made in 1944 to the laboratory of C. E. Smith in San Francisco. With Cáceres he tested

495 residents of the border states of Sonora and Baja California in the cities of Hermosillo, Mexicali and Pueblo Nuevo, 17.2 per cent reacted positively to coccidioidin.[5 7] Eliminating those who had been in the endemic areas of the United States, the percentage was 13.4.

In 1948 Glusker and his colleagues tested draftees from various states in Mexico.[5] With one exception, only the border states were represented among the positive reactors—Sonora 67 per cent, Chihuahua 37 per cent, and Baja California 32 per cent. Colima, a tropical and humid state far to the south, had 33 per cent, but the total number tested is not specified nor are former residence and travel of the subjects mentioned.

The first case which González Ochoa considers indigenous to Mexico was reported by Madrid in 1948.[4 7] Sixteen years before showing signs of pulmonary coccidioidomycosis the patient had been in Phoenix. Madrid also reported an incidence of 12.4 per cent reactors to coccidioidin among 213 residents of Hermosillo, Sonora.

In 1950, tests done by Slim Villegas and Aranda Reyes in Mexicali, Baja California, showed an incidence of 32.7 per cent positive reactions in 2,945 tests.[6 1]

At Mexico's southern extremity, González Ochoa found no positive reactions to coccidioidin in Yucatan, although 55.3 per cent of the natives reacted to histoplasmin.[477]

Northern Sonora and Baja California are very much like the endemic areas of Arizona and California in climate and physical characteristics. From a consideration of these similarities, and from his own studies, González Ochoa concludes that certain parts of northern Mexico may have as high an endemicity as California and Arizona.[501] Cases of disseminated coccidioidomycosis have been reported from Baja California, Sonora, Chihuahua and Coahuila, the four states bordering on California, Arizona, New Mexico and west Texas. The precise areas of greatest endemicity in northern Mexico remain to be defined.

## CENTRAL AMERICA

Coccidioidin and histoplasmin surveys have been undertaken in most of the countries of central America in recent years (Table V). The general pattern has been a significant number of positive reactions to histoplasmin and a tiny percentage of positive reactions to coccidioidin (0 to 4 per cent). Cases of clinical histoplasmosis have been reported from Panama, Honduras and Cuba. It is likely that in many places the high incidence of histoplasmin sensitivity is specific and that the few reactions to coccidioidin represent cross reactions to histoplasmin or some other fungus antigen, although the demonstration of clinical coccidioidomycosis in Honduras reopens the question.

TABLE V

RESULTS OF COCCIDIOIDIN AND HISTOPLASMIN SKIN TESTING SURVEYS IN CENTRAL AMERICAN COUNTRIES

| Geographic Area | Authors | Total Number Tested | | Per Cent Positive | |
|---|---|---|---|---|---|
| | | *Histoplasmin* | *Coccidioidin* | *Histoplasmin* | *Coccidioidin* |
| Panama | (1) Tucker[825] | | 151 | | 0.65 |
| | (2) Tucker[829] | 500 | 500 | 28.4 | 0.4 |
| | (3) Tucker[830] | 1000 | 1000 | 38.[illegible] | 0.8 |
| Puerto Rico | Suarez[676] | 1055 | 187 | 12.7 | 1 |
| Honduras | (1) Hoekenga and Tucker[395] | 300 | 300 | 40.2 | 4.1 |
| | (2) Scott[810] | 421 | 421 | 47.7 | 1 |
| | (3) Trejos, in preparation | | 1500 | | 25 |
| Cuba | Pardo[713] | 195 | 195 | 20.5 | [illegible].05 |
| Yucatan, Mexico | González Ochoa[77] | 150 | 150 | 55.3 | 0 |

## Honduras

The fourth general area of endemicity of *Coccidioides immitis* was demonstrated in 1951 by Castro and Trejos.[813] The first clue was their finding of *Coccidioides* in a pathologic specimen sent them from a patient in the Comayagua Valley of Honduras, where climatologic conditions are similar to those of other areas known to be the habitats of *Coccidioides*. In a skin testing survey Trejos found a 25 per cent incidence of positive reactions among 1,500 residents tested.

## SOUTH AMERICA

Two general South American areas are now known to support *Coccidioides immitis*—the Venezuelan State of Lara in the north, and the Gran Chaco Pampa region in the south, the latter comprising large parts of Paraguay and Argentina and a small strip of Bolivia (Fig. 15).

The Gran Chaco is an extensive lowland plain about 700 miles long and 400 miles wide. It is bounded on the north by the tropical woodlands of Bolivia, on the south by the Rio Salado, where it is continuous with the Pampa, on the east by the Paraguay River, and on the west by the Andean foothills. Although largely an area of scrub forest and grassland with a tropical savanna climate, there is enough variation within it to limit the area of coccidioidal endemicity. It is more humid toward the east, and more arid further inland toward the Andes. It is sparsely populated fo

the most part by men engaged in cattle raising although there is also some agriculture In the northwest oil has been discovered North of the Pilcomayo River is the Chaco Boreal or Paraguayan Chaco Its northern and western fringes are in Bolivia The Chaco Central between the Bermejo and Pilcomayo Rivers contains the Argentine Province of Formosa and the borders of Salta The Chaco Austral south of the Bermejo contains the Province of Chaco and parts of Santiago del Estero Santa Fe and Salta

The Pampa is a vast almost treeless fertile plain continuous on the north with the Chaco and on the south at the Rio Colorado with Patagonia To the east is the humid Pampa to the west the dry Pampa The latter contains a few scrubby trees and grass

## Argentina

Although the world s first case of coccidioidomycosis was described in Argentina only a handful of other cases have been diagnosed Except in sparsely settled regions its endemicity appears to be less than that in corresponding parts of North America Posadas made his brilliant observations in the years 1892 to 1900 [1] It was not till 1927 that the second Argentine case was found—that of a man from whose laryngeal lesion the fungus first called *Pseudococcidioides mazzai* was isolated [83] The third case was diagnosed as recently as 1934 [1, 6] A total of only 14 cases could be cited in a comprehensive review made in 1950 [6, 10]

At the present time there is widespread awareness of the problem Primary coccidioidomycosis and laboratory acquired infections are being recognized [49, 61] Several groups of investigators have undertaken excellent geographic epidemiologic and mycologic studies

Dr Pablo Negroni of the Malbran Bacteriologic Institute University of Buenos Aires has for many years been a leading student of the mycology of *Coccidioides immitis* In 1939 he discovered the fifth Argentine case the first from which the fungus was cultured In 1948 following the diagnosis of a case of coccidioidal granuloma in Rio Colorado Negroni and his co-workers Daglio and Briz de Negroni undertook an extensive survey of the area between the Colorado and Negro Rivers [19] Using their own coccidioidin prepared according to the method of C E Smith and standardized against his coccidioidin they tested 2 065 school children in various towns About 8 per cent of the reactions were positive and about 3 per cent doubtful The town of Rio Colorado itself had the highest percentage of positive reactions over 10 per cent

While the survey was being made Dr Briz de Negroni herself came down with cough and precordial pain and her skin test changed from negative to positive clearly demonstrating the endemicity of the area This

part of the territory of Rio Negro though considered the northern extremity of Patagonia is climatically more like the Pampa—dry and warm At present its population is sparse

A second study, conducted among the patients hospitalized in Buenos Aires showed that many of those coming from inland regions, particularly from the Chaco and Pampa had positive coccidioidin reactions[498]

In a subsequent survey of school boys in the Chaco provinces Negroni showed that the highest endemicity is in the arid southeastern corner of Santiago del Estero and the adjacent part of Tucuman[11] Half of the known Argentine cases of coccidioidomycosis have come from this small area[63] Negroni demonstrated an incidence of 20 per cent positive reactions to coccidioidin in Las Termas Santiago del Estero

In a series of thirteen papers published in 1948 1953 Negroni reported his exhaustive and original studies of *Coccidioides immitis*—its biochemical characteristics[illegible] its gross and microscopic morphology[illegible] the essential similarity of North American and Argentine strains[493] variations in virulence among strains[494] geographic distribution[63] immunologic characteristics[348] and cytology[4]

Professor Flavio L Niño Professor of Parasitology at the University of Buenos Aires has also been active in the investigation of Argentine coccidioidomycosis In 1931 he identified the causative organism of the third known Argentine case In 1949 he undertook a study of patients hospitalized in the Hospital Nacional de Clinicas in Buenos Aires[61] His colleague Luis Ferrada Urzua made a simultaneous study in hospitals in Cordoba and Tucuman They concluded that there are in general three areas of endemicity in Argentina one on the North (the Chaco) a second in the Central Provinces (Tucuman Catamarca Cordoba Santiago del Estero and San Luis) and a third in the south (Rio Negro) More recently the central focus has been enlarged to include Mendoza[63] There may be continuity between the known areas of endemicity forming a great inland semi circle through the Bolivian Paraguayan and Argentine Chaco the Pampa and northern Patagonia

## Paraguay

One of the best South American epidemiologic surveys was conducted by Dr Raul F Gomez a physician for the Union Oil Company during its early operations in a new and sparsely inhabited area of Paraguay where conditions for a controlled study were excellent[4] The investigation was initiated by the recognition of two cases of primary pulmonary coccidioidomycosis with erythema nodosum not often diagnosed in South America

Paraguay is split into western and eastern parts by the great Paraguay River In the eastern section where all the principal cities are located

surveys of coccidioidin sensitivity have shown few positive reactions At the capital city of Asuncion Gines and his co workers reported an incidence of only 2 6 per cent The western part of Paraguay—almost twice as large as the eastern—comprises the Paraguayan Chaco a vast low plain whose monotonous flatness is broken only by a few small hills in the far north The climate is hot and arid the summer temperatures often reaching 110 F or more High winds blow from the north during most of the year To the south and east the Paraguayan Chaco is so low that it is flooded yearly by the Pilcomayo and Paraguay Rivers Here it is covered by palm groves and tall grass Cattle ranches and irrigated farms predominate Lengua Indians and other aboriginal tribes inhabit the area The middle zone of the Paraguayan Chaco is very different Although fairly heavily wooded and subject to rains part of the year there is no grass to prevent the blowing about of the thick dust in the heavy winds In the northwestern corner of Paraguay adjacent to Bolivia is a third zone an empty desert were wind blown sands pile high in dunes There is almost no rain temperatures are torrid and the strong north wind rarely rests Nothing grows but a few scrubby bushes and cactus plants Guazurangue Indians live here as they have for generations unknown The area is otherwise unpopulated except for outpost military garrisons and oil company personnel

In coccidioidin surveys conducted in the three zones of the Chaco Gomez discovered a sharply increasing endemicity from southeast to northwest Only 2 per cent of the Lengua and Sanapana Indians in the grassy southeast reacted to coccidioidin In the northwestern desert 44 per cent of the Guazurangue Indians reacted Paraguayans in intermediate areas showed 15 5 per cent positive reactions

## Bolivia

Because of the proximity of Bolivia to the known areas of high endemicity in the Paraguayan and Argentine Chaco it is likely that the fungus exists there too No formal studies have been carried out but there are a few hints that at least part of Bolivia is endemic In his survey of Paraguay Gomez found that the incidence of positive coccidioidin reactions was highest near the Bolivian frontier [8] In a publication concerning the biology of *Coccidioides immitis* Artagaveytia Allende of Montevideo mentions that one of his strains was isolated in La Paz Bolivia from a man who had lived in the Chaco [11]

## Venezuela

For more than half a century only two general habitats of *Coccidioides immitis* were known the first in southern South America and the second

in southwestern North America (United States–Mexico) The third important area was discovered in 1949 in the Venezuelan State of Lara Profiting from the long experience of other regions Venezuelan physicians speedily applied modern epidemiologic methods so that within a year the endemicity of coccidioidomycosis in Estado Lara was demonstrated beyond doubt

The Venezuelan discovery was occasioned by the diagnosis of coccidioidal granuloma of six years duration in a 60 year old woman who had always lived in the State of Lara [16] The case was studied by Dr Humberto Campins Chief of the Dermatological Service at the Antonio Mario Pineda *Hospital in Barquisimeto and his colleagues Dr Modesto Scharyj and* Señora Vera Gluck The lesions contained spherules the coccidioidin skin test was positive and the complement fixation test done by Dr C E Smith was positive at *1 16*

In March 1949 Dr Campins saw a second case of disseminated coccidioidomycosis [16] Within months he had undertaken and completed one of the best coccidioidin surveys ever made [4] Over 7 000 residents of seven districts of Lara were skin tested using coccidioidin supplied by Dr C E Smith and by Dr Negroni of Buenos Aires In the capital of Barquisimeto alone nearly 4 000 tests were done The percentage of positive reactions varied from 1 1 in Cabudare to 46 4 in Aguada Grande The over all percentage was 10 4 Over three quarters of those reacting positively had never resided outside of Lara A break down of the figures obtained from testing 2 450 school children and young adults showed that *the percentage of positive reactors steadily increased from 6 per cent at* 5 years of age to 15 per cent at 25 years of age

The State of Lara in the northwestern part of Venezuela is essentially a large plain *surrounded by mountains It is fairly hot and arid and* vegetation consists almost solely of cactus and other desert plants The annual rainfall is about 18 inches per year at Barquisimeto and somewhat less in other parts of the state *Being in the tropics only 10 degrees from* the equator it has only two seasons–the rainy (April–October) and the dry (November–March ) The tropical heat is moderated by the altitude of most of the inhabited areas *so that in general Lara is more humid* and not quite so hot as other desert areas where coccidioidomycosis is endemic The similarity between the State of Lara and several other Venezuelan states suggests that the fungus may exist *elsewhere as well*

## Uruguay

Dr Juan E MacKinnon of the University of Montevideo has been responsible for many of the advances in the study of fungus diseases in *South America not only in Uruguay* but also in other countries He and

his colleagues Ricardo C Artagaveytia Allende and Hector Vinelli were pioneers in the use of coccidioidin skin testing in epidemiologic studies in Uruguay Paraguay Chile and Argentina [6] Their coccidioidin made after the method of C E Smith is now a standard preparation in South America In 1941 they tested their first hundred Uruguayan subjects with coccidioidin supplied by Smith finding only one doubtful reaction With their own coccidioidin 1 100 they obtained only 9 positive reactions in 977 trials (0 9 per cent) With a 1 10 dilution the percentage rose to 4 6 There was no significant difference among residents of various parts of Uruguay The country is relatively small and its climate fairly homogeneous MacKinnon and his co workers having shown cross reactions between histoplasmin and coccidioidin in experimental animals felt that even their low proportion of human reactors to coccidioidin was falsely high Histoplasmin sensitivity was therefore also determined in 360 subjects with 10 5 per cent positive reactions Only one of the 360 reacted to coccidioidin and he had a much stronger reaction to histoplasmin than to coccidioidin They concluded that coccidioidomycosis is not endemic in Uruguay although histoplasmosis probably is

## Chile

Although Chile is adjacent to Argentina and also has a diversity of climates—arid and semi arid—coccidioidomycosis is not known to occur there Coccidioidin skin surveys have been done in several areas without the discovery of any positive reactions In 1950 Ferrada Urzua Alonso and Donoso reported a survey of 332 subjects from 26 cities (mostly from Santiago Arica and San Bernardo) [6, 7] In 1951 MacKinnon and Honorato Chaparro tested 400 school boys in Vina del Mar [8, 9] In 1952 Vacarro and Ferrada Urzua studied the skin sensitivity of 95 students at the University of Chile [718] In all of these surveys there was but one positive reactor—a college student from Venezuela

## Brazil

Not many areas of this vast country have been studied systematically but so far coccidioidomycosis is not known to be endemic in Brazil Surveys with histoplasmin coccidioidin and paracoccidioidin in the city of Rio de Janeiro have showed up to 30 per cent reactions to histoplasmin but only 1 per cent to coccidioidin [31] The latter were considered cross reactions to others antigens

## Ecuador

Negroni mentions an endemic focus at Pomasqui Ecuador [763] More data are necessary before accepting it as a valid area of endemicity

## EUROPE

Although several cases of coccidioidomycosis have been reported from European countries, it is unlikely that continental Europe is a natural habitat of *Coccidioides immitis*. Until recently, the only studies of the disease concerned individual cases. Coccidioidin skin testing surveys—although limited in scope and number—are now confirming the opinion that *Coccidioides* is not among the fungi to be found there.

### Italy

The first European series of cases was recorded in Italy, where Ciferri and Redaelli have made extensive studies of the mycology of *Coccidioides immitis*.[193, 99] The fungus was isolated from three patients resident in Naples. The first was a girl of 14, who had a pulmonary cavity with recurrent cough, blood streaked sputum, and pleurisy for 7 years.[99] A man of 40, working in the grain silos at Naples, was reported to have similar symptoms in the same year (1929).[99] "*Blastomycoides*," later shown to be identical with *Coccidioides*, was found in the sputum of both. One might conjecture that the finding of one or two patients with residual pulmonary coccidioidal cavities represents a much higher incidence of primary coccidioidomycosis.

In 1933 a Neapolitan woman is said to have had gluteal swelling and ulceration after a local injection of camphorated oil.[99] *Ctenospora meteuropaea*, later identified with *Coccidioides immitis*, was isolated. The true sequence of events can only be inferred. Trauma may have caused a localized lesion in a disease already disseminating.

A case of pulmonary coccidioidomycosis reported in 1955 was thought by Sotgiu and Corbelli to have been due to contact with agricultural products originating in the United States.[illegible]

It is unlikely that coccidioidomycosis is endemic in Italy, although definitive studies have yet to be done. The sporadicity of reported infections suggests that fomites, rather than natural exposure, were responsible. Preliminary reports of skin testing surveys support this view. No reactions to coccidioidin were observed, for instance, among 145 school children of Toscana.[illegible]

### Hungary

A case of coccidioidomycosis occurring in a rabbit from the vicinity of Budapest was reported in 1954,[illegible] and two cases of coccidioidal disease in human beings were reported in 1955.[illegible] The photographs of the organisms and some of the studies are not conclusive, but the findings were so suggestive to the authors that they proposed a coccidioidin skin survey

of the population near the Austro Hungarian border Without further information the endemicity of the disease in that vicinity seems unlikely

## France

Preliminary surveys with histoplasmin and coccidioidin show nothing unexpected Among 463 tuberculous patients in a sanitarium there were no definitely positive reactions to either histoplasmin or coccidioidin [6] Eight men had doubtfully positive reactions to coccidioidin so weak that no inferences may be drawn In another survey in northern France there were no positive reactions among nearly 600 adults and children [5, 4]

## Norway

Coccidioidin and histoplasmin testing of 1 074 subjects in Norway showed 27 reactions to histoplasmin alone three to coccidioidin alone and 23 to both reagins [739] Of the three reacting positively to coccidioidin alone one had been in California It is possible that histoplasmosis was responsible for some of the reactions The insignificant number of reactions to coccidioidin alone would be expected in the damp Norwegian climate

## Finland

Histoplasmin and coccidioidin studies in Helsinki revealed no significant reactions [83]

## AFRICA

The question of endemicity of coccidioidomycosis in the Belgian Congo was raised briefly when a European colonist contracted a fungus infection caused by an organism resembling *Coccidioides immitis* [7, 9, 3, 761] The disease was later called African histoplasmosis and the organism *Histoplasma duboisii* Vanbreuseghem 1952 Some mycologists consider it to be a variant of *Histoplasma capsulatum* In one area skin testing surveys showed 17 per cent positive reactions to histoplasmin and 6 9 per cent to coccidioidin the latter probably representing cross reactions

## ASIA

## India

In a study of 64 patients from Calcutta with eosinophilia and pulmonary calcifications no positive reactions were found to coccidioidin histoplasmin or blastomycin although all reacted to tuberculin [808]

## Philippines

Studies of 824 patients in a tuberculosis hospital near Manila showed no reactions to coccidioidin although 26 (3 15 per cent) reacted to histo

plasmin[719] It is fortunate considering the devastating effects of *Coccidioides* in Filipino patients, that the Philippine climate will not support the parasite

## OTHER PARTS OF THE WORLD

Isolated cases of disseminated coccidioidomycosis have been reported from the Balkans Holland China Hawaii and Canada Some of the diagnoses were erroneous for no cultures were obtained and the description of the organism found on histologic study is unconvincing The fungus obtained by culture from the Balkan patient was clearly *Coccidioides immitis* but there is no evidence that the infection was indigenous In such isolated cases, fomite transmission is at least as likely as endemicity

Doubtless other areas of endemicity will be discovered for apparently compatible terrain and climate exist on several continents The tools are available Further knowledge merely awaits using modern epidemiologic methods in other parts of the world

Chapter Five

# Epidemiology of Coccidioidomycosis



## ECOLOGY OF *COCCIDIOIDES IMMITIS*

*C occidioides* thrives on such simple substrates and tolerates such extremes of temperature and pH that it might be expected to be ubiquitous As a matter of fact its geographic limitations are more severe than those of any other important pathogenic fungus There are evidently other than chemical and thermal requirements which delimit its habitat

Friedman and her associates[9, 7] measured quantitatively the number of coccidioidal spores surviving under various conditions of temperature and humidity Temperatures of −15° C to +50° C were used Temperatures less than 37° C had little deleterious effect Low relative humidity (10 per cent) together with high temperatures (37° C) were lethal but only after six months At 50° C all spores died in two weeks The striking thing about these data is not that the fungus can finally be killed by extreme conditions but that it survives as long as it does In external nature the combination of high temperature and low relative humidity is short lived—not only seasonally but also diurnally During part of every 24 hour period the temperature is cool and the relative humidity moderate or high Because it *can survive the hot dry hours of the day as* can few other micro organisms *Coccidioides* is adapted to desert climates

Lubarsky and Plunkett have shown that *Coccidioides* will grow on almost any soil within almost any natural pH range and under almost any natural extreme of heat and cold.[86] They inoculated mycelial elements of the fungus into many different samples of soil ranging from rich loam to almost pure sand obtained from California, Arizona, New York, New Jersey, Pennsylvania, Oklahoma, Colorado and Texas. Every sample supported the growth of *Coccidioides*. Even the sifting of sandy soils to remove particulate vegetable matter did not restrict growth so long as moisture was present. The organism also grew on the vegetable particles separated from the soil. In soil the fungus remained viable after four months of constant exposure to a temperature of 42° C or to alternating freezing at −20° C and thawing at room temperature. Growth occurred at pH levels ranging from 3.5 to 9.0, a range covering the pH of most soils. Obviously, *Coccidioides* is not fastidious under laboratory conditions. Yet in external nature, its domain is narrow.

Plunkett has noted that *Coccidioides* thrives better in uncultivated soils than in cultivated, presumably because of the increased organic content of the latter and consequent competition with other micro-organisms.[5, 4]

Smith and his associates[4] have demonstrated that the incidence of primary coccidioidomycosis varies directly with the amount of rainfall during the previous winter. At the air fields of the southern San Joaquin Valley during World War II, dry winters were followed by a low incidence of coccidioidal infections and wet winters by a high incidence. Their studies are supported and elaborated by the findings of Egeberg and Ely who demonstrated the difference in the distribution of *Coccidioides* in the soil after the dry season and after the wet season.[8] Studying samples of San Joaquin Valley soil taken at varying depths below the surface, they noted that coccidioidal growth was concentrated on the surface at the end of the wet season (April) whereas at the end of the dry season (January) there was less growth at the surface than at depths of 4 to 12 inches. Furthermore their percentage of positive cultures at the end of the wet season was almost three times that which they found at the end of the dry season. They postulated that the heat of the summer sun reduced surface growth during the dry season.

Certain of these data appear contradictory. *Coccidioides* will grow under almost any condition in the laboratory—yet in external nature its habitat is limited. It thrives best on rich media—yet in the desert it is most often found on the leanest soil. The only deleterious laboratory condition is the combination of high temperature and low humidity—yet it is precisely in areas where such a condition obtains that the organism flourishes.

Egeberg and Ely[9] have suggested an intriguing theory to resolve these paradoxes. They point out that *Coccidioides* grows much more readily in sterilized soils than in unsterilized. Perhaps heat and low humidity abet the growth of *Coccidioides* by sterilizing the soil. Poor substrates, high temperatures and low humidities may slightly retard *Coccidioides*—but they completely kill its rivals. "Could it be," they ask, "that this scorching, sterilizing summer heat is an ally of the organism by giving it, for a brief period of time, a growth medium not thoroughly contaminated with its antagonists and competitors?"

The role of animals in the ecology of *Coccidioides* has not been definitely established. It is generally thought that animals, like man, are but accidental hosts of the parasite, although Emmons for a while felt that there may be more than a casual relationship.[347] In 1942, when he discovered coccidioidal infections in several species of rodents in the Arizona desert, particularly in pocket mice (*Perognathus*) and kangaroo rats (*Dipodomys*), he proposed that coccidioidomycosis is primarily a disease of such rodents, transmitted only incidentally to other animals. He has more recently modified this opinion, no longer considering rodents to be necessary reservoirs of infection.

In their studies of *Coccidioides* in the soil of the southern San Joaquin Valley, Egeberg and Ely found a considerably higher percentage of positive cultures in soil taken from rodent burrows than in that collected at random at least five feet away from the burrows.[91] In a total of 500 soil samples, 13.6 per cent of those from burrows were positive, but only 3.4 per cent of the random samples. The reason for the higher concentration of *Coccidioides* in burrows is not clear at present. Factors may be (1) higher relative humidity and lower temperatures and (2) "enrichment" of the medium like that of the barnyard soil in which *Histoplasma* has been found in Tennessee. In any case there seems to be some relationship, casual or otherwise, between the fungus and desert rodents.

In a meticulously careful study of ecology and climatology, Maddy[349] has demonstrated that the area of endemicity of *Coccidioides immitis* is almost synonymous with the Lower Sonoran Life Zone. By subdividing the zone even further, he has been able to grade with nice precision the variations of endemicity within the area. On the basis of his ecologic studies he predicted the high rate of infection in one southwestern city even before he knew that clinical experience confirmed his judgment.

Some of the common plants of the Lower Sonoran Zone are the creosote bush, mesquites, cacti, yuccas and agaves. Among the characteristic mammals are the kangaroo rat, pocket mouse, long-eared desert fox and the big-eared and tiny white-haired bats. Some of the distinctive birds are the mockingbird, road runner, cactus wren, canyon wren, desert

thrasher, hooded oriole, black-throated desert sparrow, Texas nighthawk and Gambel's quail. It appears that *Coccidioides immitis* may be added to the list of indicator flora for the zone.

## CLIMATOLOGY OF COCCIDIOIDOMYCOSIS

A comparison of the widely separated areas where *Coccidioides* is endemic makes its climatologic requirements clear. There is a fairly narrow spectrum of conditions under which it multiples in external nature. Even within the Lower Sonoran Life Zone there is considerable variation in the concentration of the fungus, and certain extremities of the Lower Sonoran, like the Sacramento Valley of California, appear to be free.

*Coccidioides* exists in areas that are semi-arid, but not completely dry. It prefers the edge of a desert region rather than its center. It needs rain, but prospers best when precipitation is restricted to the winter months, to be followed by a long dry summer. The amount of rain is not so critical as its confinement to a short season. In the San Joaquin Valley rain averages less than 10 inches per year. In the central Paraguayan Chaco it may reach 20-28 inches per year. Coccidioidal infections seem to be more prevalent when dry seasons follow fairly rainy winters.

High summer temperatures and mild winters are also necessary. The average daily high temperature in July at Bakersfield in the southern San Joaquin Valley is 100.2° F. At Fresno, 100 miles north, it is 99.0° F. That small difference may partly explain the higher endemicity in Kern County. In the winter, freezing temperatures are reached relatively infrequently. The average daily low temperature in December at Bakersfield is 35.2° F and at Fresno 38.1° F.

A fairly fine light soil capable of generating clouds of dust also prevails in endemic areas. Winds are not necessary for growth of the fungus, but they obviously aid dispersion of its spores. The Paraguayan Chaco is almost constantly windy. The San Joaquin Valley has windy months, but during much of the year the air is fairly quiet. Wind, however, is not the only factor in raising dust. The volume of dusty air need not be large. The size of the dust cloud is irrelevant so long as it envelopes the face of a susceptible individual. Because agricultural procedures—whether driving a tractor or picking cotton from a dusty plant—raise dust where people are, such work is more important than high winds.

In summarizing the physical environment in which *Coccidioides* may be dangerous, Egeberg has cited these factors: hot summer weather, mild winter weather, a rainy period during the year, three or more months without rain during the year, soil productive of much dust, and winds to scatter the dust.[793]

## NATURAL EXPOSURE IN ENDEMIC AREAS

Since inhalation of one lungful of spore bearing air is all that is necessary to contract coccidioidomycosis mere presence in an endemic area constitutes a hazard of some degree Tourists spending but a few hours driving through such an area have been known to become infected On the other hand some people have lived all their lives near the fungus without having the disease

Several factors affect the concentration of the fungus in the air of an endemic region The first factor is ecologic i e the amount of the fungus growing naturally in the vicinity Because the spore is microscopically small one can only infer where it is being propagated The fungus probably multiples during the rainy season and is dispersed during the dry season when spores break from the mycelia and are scattered by the wind

A second factor affecting the number of air borne spores is the degree of artificial alteration of the ecology i e the relative proportion of bare ground and paved or grass covered ground Cities are less dusty than countrysides A moderate summer breeze in the city may be a dust storm in the country Alterations in the vegetation clearly cause changes in the fungus population or in its dissemination throughout the atmosphere

Military operations during World War II gave the most striking demonstration of the importance of vegetation In 1941 several air fields were established in the southern San Joaquin Valley Coccidioidal infection was recognized to be a hazard but it was preferred to the hazards of mountains and fog in alternative locations During the first year clouds of dust billowed over the fields and a quarter of the susceptible personnel became infected C E Smith appointed consultant to the Secretary of War proposed rigid dust control measures [477] Roads were paved air strips were hard surfaced and swimming pools were substituted for dusty athletic fields Lawns were planted by the acre and military personnel were ordered at risk of court martial to avoid unprotected areas as much as possible As a result of these efforts the rate of coccidioidal infection in the military installation was cut by one half to two thirds at the same time that the rate in surrounding agricultural camps was rising

## SEASONAL VARIATION IN THE INCIDENCE OF PRIMARY INFECTIONS

Although primary coccidioidomycosis occurs throughout the year its incidence increases sharply in early summer and remains high until the first rains of winter C E Smith has nicely shown that the monthly rate is inversely proportional to the amount of rainfall (Fig 18) [273] In the San Joaquin Valley primary coccidioidomycosis is essentially a disease of

June to December, the peak occurring about September. The incide
is usually lowest in February. In some years the season begins in \
or even earlier and sometimes it continues into January. A few inf
tions begin during the rainy season for even then dry days may be win
and dusty.

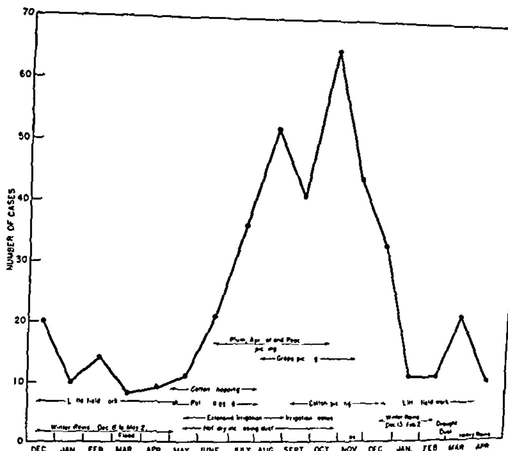



Figure 18 Seasonal variation in the incidence of primary coccidioidomycosis Kern and Tulare Counties California December 1937 to April 1939 (From Smith *American Journal of Public Health* 30 600 611 1940 )

## OCCUPATIONAL EXPOSURE

For 60 years it has been obvious that certain occupations predispose to coccidioidomycosis more than others. The reason is clear: the greater the exposure to dust the greater the hazard. Of paramount importance are agricultural pursuits which not only draw people to soils rich in spores but also stir up the dust bearing those spores. The first cases in California occurred in agricultural workers. In a survey of 100 cases of coccidioidomycosis in Fresno California the author found that half of the patients had been engaged in farm labor (tractor driving, cotton

picking grape picking etc ) just prior to the onset of the illness Five more worked in cotton gins or compresses where the air was heavy with dust brought from the fields on the cotton bolls Another nine did construction work or general labor in the same dusty areas Truck drivers accounted for another four Over two thirds therefore worked in the fields or rural areas or dealt with their products The remaining third represented a cross section of community life many of whom had also driven out into the country for business or pleasure

Agricultural employment notoriously attracts non immune people to endemic areas The early epidemiologic study of acute coccidioidomycosis with erythema nodosum done by C E Smith in 1937 1939 showed that over four fifths of the cases occurred in people born outside of the endemic area [3] Nearly half of the patients had been in the San Joaquin Valley less than a year and nearly two thirds for less than two years Smith s study was done during the period of migration of many thousands of farm workers from Oklahoma and Arkansas to California Primary coccidioidomycosis occurred overwhelmingly in groups newly attracted by the agriculture of the endemic area Furthermore it is members of the races most susceptible to progressive coccidioidomycosis who are now most likely to enter endemic areas at the call of agriculture Each year thousands of seasonal farm laborers enter the San Joaquin Valley from Mexico—many of them legally by agreement between the United States and Mexico and some illegally—the wet backs" who evade normal immigration procedure Epidemiologic surveys in Mexico are made difficult because so many Mexicans who react to coccidioidin have previously been in the *southwestern United States* Large numbers of Negro farm workers have come to California for employment in cotton fields The southern San Joaquin Valley also has several large colonies of Filipinos who work in the grape vineyards and fruit orchards Most cases of severe dissemination occur among members of these dark skinned races

Recognition of coccidioidomycosis as an occupational hazard is nothing new In 1937 the State Department of Public Health reported that of the 450 cases of coccidioidal granuloma previously diagnosed in California 65 5 per cent had occurred in people whose jobs exposed them to the soil and its products In the same year Gifford Buss and Douds wrote

> For some time it has been recognized by those dealing with the disease that agricultural workers cattle and sheep men oil riggers telephone post diggers and other persons with occupations involving exposure to soil dust in the San Joaquin Valley and Southern California counties are more exposed to risk of infection with the *Coccidioides* fungus than elsewhere in the state The disease is now recognized by insurance companies as an occupational hazard for workers who are exposed to soil dust in endemic areas

The first case to receive compensation in Kern County was a geologist for the Shell Oil Company in 1930.[10]

Outside of the endemic areas, it may be relatively easy to establish occupational exposure in such infections as those acquired in the laboratory or by handling fomites. Scarcely less difficult is the determination of responsibility for infections suffered by employees who in the course of their occupation are required to enter endemic areas. Most problems arising in endemic areas are more complicated, for mere residence implies a certain hazard, as Levan has emphasized in a thorough review of occupational responsibility in coccidioidomycosis.[11] Legal assumption of occupational origin in an endemic area requires evidence that the occupation increases the risk of infection over that of other members of the community. Absolute proof that infection is contracted on the job is not demanded, for uncertainty of proof does not destroy a legal right. It is sufficient to demonstrate that the probability of infection is greater during working hours than it is during the rest of the day.

Most often the question of occupational origin involves workers who were residents of endemic areas prior to their employment. The question is then merely one of probabilities. The exact instant of exposure can obviously not be determined. It is necessary to show that the employment exposes the worker to a greater hazard of infection than that of the community in general. The problem resolves itself essentially to this question: Where was he in contact with the greatest amount of possibly contaminated dust—on the job or off? The probabilities of exposure in different situations are roughly proportional to the amounts of dust encountered in each.

In one such case, a 29 year old white farm worker moved from Oklahoma to the San Joaquin Valley of California in 1950. In the next four years he lived in various parts of the "west side" of Fresno County, where coccidioidomycosis is endemic. Part of the time he worked in the fields, but during the cotton picking season he worked in cotton gins.

In 1954 he lived in a house surrounded by lawn, where dust was present but not unusually heavy. He drove five miles over slightly dusty roads to the cotton gin where he worked 12 hours every night. The air was so heavy with dust and lint brought in by the cotton that the floor had to be swept once or twice every hour. The conditions were not particularly different from those of other seasons.

After about four weeks' work he was stricken with chest pain, malaise, night sweats, and a dry cough. When he was hospitalized five days later, *Coccidioides* was cultured from the sputum. His fever and other symptoms cleared after four more days, but an acute cavity appeared in the area

of pneumonitis requiring three months of rest before it closed spontaneously The Industrial Accident Commission of California found the infection to have been contracted in the course of his employment

Levan[811] has suggested these criteria for establishing a case as occupational

(1) Evidence that the patient was free of the disease prior to the suspected employment exposure

(2) Chronologic compatibility between the alleged infecting exposure and the onset of the disease

(3) Working conditions clearly productive of possible infecting exposures

(4) Exclusion or evaluation of extra employment exposure of an equal or greater degree than work exposure

## FOMITE TRANSMISSION

Because of the ease with which dust may be carried on clothing and other articles fomite transmission of *Coccidioides immitis* is easy to imagine On the other hand in the individual case it is very hard to prove and few cases are reported Within endemic areas where the very air may be contaminated cases involving fomite transmission could not be distinguished from others Outside endemic areas primary infections would likely not be diagnosed and secondary disease would appear long enough after exposure to make identification of the offending fomite all but impossible

There are nevertheless a few data which demonstrate that fomite transmission is real Children have contracted acute coccidioidomycosis by playing with cotton bolls brought from endemic areas Men have been infected by handling dusty clothes An epidemic reported by Plunkett is perhaps the most striking example of the roles of fomites[914] Several anthropology students from Los Angeles had dug into the soil of an old Indian campsite in the uninhabited desert near Inyokern California for artifacts Two weeks later four of the group and another student who merely cleaned the artifacts after they were brought back to the laboratory were stricken with acute pulmonary coccidioidomycosis Soil samples from the campsite gave positive cultures for *Coccidioides immitis*

Additional evidence concerning the importance of fomites is supplied by the number of cases of coccidioidal granuloma which have occurred in areas where fomite transmission is more easily postulated than endemicity The validity of some of these cases is questionable for cultural and immunologic data were never obtained the diagnosis being made only from post mortem observation of pathologic sections In others the identity of the fungus was reasonably well established In any event

there have been a few certain and many possible cases of coccidioidomycosis in non endemic areas Furthermore it has been established that many of the patients concerned could never have travelled in endemic areas Such cases have occurred in many of the non endemic states of this country and in Canada Hawaii Italy and the Balkans

In recent years the question of fomite transmission has been raised several times in the literature In 1949 a wool sorter in New England died of acute miliary disseminated coccidioidomycosis One account of his case says that he was in California several years previously [6a] although another account denies this [6] His work involved handling dusty wool some of which was from California The sequence of events is not clear, but it is possibly a case of fomite transmission

Bennett Milder and Baker cited the case of a Negro never outside the northeastern states whose occupation involved handling a hemp product imported from California and Mexico In 1949 he was stricken with chronic progressive coccidioidomycosis The authors concluded that fomite transmission of the fungus was the most likely source of his infection [7]

Other cases less well defined suggest that dust on fruit and vegetable products may have transmitted coccidioidal spores The question is still open

## LABORATORY EXPOSURE

The only occupations more hazardous than agricultural and allied pursuits are those which involve handling *Coccidioides* in the laboratory The total number of laboratory acquired infections is unknown because many must be asymptomatic or undiagnosed A number of severe infections are nevertheless a matter of record

It is easy to see why *Coccidioides* is a dangerous organism to handle It grows on a wide variety of media requiring no special conditions so that if present in cultured material it will appear whether or not it has been expected Its colonies are not so distinctive but what they can be mistaken by the unsuspicious for those of less dangerous fungi Mature cultures fragment readily into chlamydospores and arthrospores so tiny that they are wafted with the slightest air current easily passing through such barriers as protective masks and being borne unseen for great distances Colonies usually do not bear arthrospores and chlamydospores on the aerial mycelium until they are several days old In the first day or two they are therefore relatively harmless but after air borne spores develop there is no absolutely safe way of handling them Unless the technician is dealing constantly with *Coccidioides* he may not suspect its identity in the culture until he has opened it mounted it for microscopic study and otherwise liberated its spores

We can surmise that unrecognized infections often occurred in the early years when the fungus was cultured by workers blithely unaware of the portal of entry, the pathogenesis of the disease, and the infectiousness of the spore. The first recorded case was that of a Nebraska physician, the course of whose disease was reported in three papers by Tomlinson and Bancroft in 1928 and 1934.[93, 6, 19] As a medical student he had worked with cultures of *Coccidioides* in 1927, suffering a typical primary infection soon followed by dissemination to the left leg and foot. Fortunately the disease was not fatal.

It will be recalled that it was an infection acquired in Dickson's laboratory which first suggested to him that there is a mild form of coccidioidomycosis.[8] Numerous other infections were later recognized in the laboratories at Stanford University, some showing only conversion of coccidioidin skin tests from negative to positive and others being associated with symptoms and spherule-containing sputum. On one occasion 13 obstetrics students who had been in a classroom two stories above the laboratory contracted primary coccidioidomycosis.

Cases have occurred in most of the California laboratories handling the fungus, but at the present time its danger is so well recognized there that adequate precautions are usually taken. It is in non-endemic areas that the hazard is now greatest. In 1943 Bush of Tuscaloosa, Alabama, reported the case of a medical technician who worked with pathogenic fungi.[344] While preparing a mount from an old culture of *Coccidioides* she dropped the cotton plug to which long hyphae were adherent. As it struck the table a cloud of dust arose. Although she had worn a surgical mask which covered her mouth and nose well, two weeks later she suffered an acute febrile illness with erythema nodosum and arthritis, and the coccidioidin skin test became strongly positive.

The fatal case of a 74-year-old Negro male dishwasher was reported by D. T. Smith and E. R. Harrell, Jr., of Duke University in 1948. After collecting glassware from the mycology laboratory and delivering it to the autoclaving rooms, the patient suffered an acute pneumonia, proved to be coccidioidal when the fungus was recovered from the sputum. Generalized lymphadenopathy and meningitis characterized a progressive disease which was fatal in 170 days.

In the same year Nabarro of London reported the case of a 32-year-old research chemist who prepared extracts of *Coccidioides* for skin testing by scraping dry cultures into a receptacle and grinding them with saline.[490] So much dust was raised that she wore a gauze mask, but a week later she came down with acute pneumonia, erythema nodosum and arthritis. *Coccidioides immitis* was recovered from an inoculated guinea pig.

Gonzalez Ochoa in 1949 mentioned two infections acquired in his laboratory in Mexico City, one characterized by bronchitis and the other by erythema nodosum.

In 1950 Looney and Stein reported the case of a 28 year old *Negro* technician who contracted an acute illness 2 weeks after examining with a hand lens an open culture later identified as *Coccidioides immitis*.[9] The mycosis became disseminated to the bones of the hands and feet.

In a review of 1 342 laboratory infections caused by various pathogens Sulkin in 1951 noted that 63 were caused by fungi—usually *Coccidioides*.[6] In addition to the cases reported in the literature Smith has collected a total of 63 proved and 9 probable cases of laboratory infections.

In 1952 Izzo Bonfiglioli and Martinez reported the first laboratory infection in Argentina.[91] A technician was discovered to have nodular lesions in both lungs. In retrospect he recalled an illness with cough, retrosternal pain and erythema nodosum. The coccidioidin skin test was positive.

In reviewing the reports of laboratory acquired infections in non endemic areas one is struck by the fact that almost all of the patients had either erythema nodosum or disseminated lesions. Inasmuch as these complications occur in only a small minority of infections it is obvious that the total number of cases must be very much larger than reported. The implication is clear: *Handling* Coccidioides immitis *without proper precautions is foolhardy—and for members of certain races may be suicidal.* The danger may be minimized by certain precautionary measures more fully described in Chapter Three, such as use of liquid media, sealing of cultures on solid media after arthrospores have had a chance to develop and use of bacteriologic hoods or other protective devices.

## THE QUESTION OF CONTAGIOUSNESS

The problem of the communicability of coccidioidomycosis arose when the first patient was seen in California. Even before his hospitalization he was effectively isolated by fear, for his fellow workers shunned his presence completely. Although data are now adequate to answer the question once for all, it continues to harass patients, their families and their physicians, particularly *outside of endemic areas*. The question is intensely practical. I once observed a patient with slowly progressive chronic *dissemination* who had a large subcutaneous "cold abscess" of his back with a tiny draining sinus but whose lungs were long since perfectly clear. Well able to be up and around, he was unrestricted in his hospital privileges. When transferred to a mid western hospital in order to be near his family he was isolated so energetically that he was all but abandoned by the terrified staff. His confusion at the sudden banish

ment was complete A week later he signed his release against medical advice Inasmuch as strict isolation presents a morale problem under the best of circumstances it is defensible only when it is necessary to protect the health of others

As Berke has stated the problem

> The significance of this difference of opinion is greater than mere academic controversy It is of vital importance to the patient and his family to know that isolation (such as is indicated in tuberculosis) is unnecessary In fact since the patient with residual lesions including cavities generally has few if any symptoms and is well able to engage in gainful employment the entire matter of socioeconomic adjustment becomes dependent on the question of infectivity of his disease [89]

Before the nature of the causative organism was understood confusion about the problem of transmissibility was understandable When the distinction between the two phases of *Coccidioides immitis* was recognized fear of contagiousness was in large part allayed It was observed that it was in the mycelial or saprophytic phase that the fungus was infectious As long as it was thought that mycelial forms never occurred in animal tissues it was generally accepted as a corollary that the disease could not be spread from a patient to his friends and relatives Occasional critics of this view felt that the parasitic form or spherule was also infectious In a series of studies of the question Rosenthal showed that guinea pigs could be infected if material containing spherules was forcibly injected into the lungs through a tube placed in the trachea [451] No one doubted Rosenthal s observation but most students felt that the conditions of the experiment were not analogous to the clinical situation but were analogous to experimental introduction of spherules into other parts of the body Examples of human infections from implanting spherules into abraded tissues are exceedingly rare In a subsequent paper Rosenthal reported that healthy guinea pigs became infected if they were caged with diseased animals [6] an observation that has not been confirmed by others In general it has been felt that except under artificial conditions the spherule is not an infective agent and that there is therefore no danger of transmission of the disease from patients who harbor only the spherule form

The question of contagiousness was reopened when it was discovered that the mycelial form of the fungus may appear in benign residual pulmonary cavities and granulomas On the basis of pathologic study of a case or two some writers have concluded that coccidioidomycosis must be considered a contagious disease [5, 0, 6, 8] It is noteworthy that fear of communicability has been expressed not by writers who live in endemic

areas, but by those who live elsewhere and who are therefore likely to see only sporadic cases.

When my colleagues and I first reported the discovery of hyphal elements in the sputum of patients with coccidioidal cavities of the lung,[53] it was realized that the question of contagiousness was thereby raised even more poignantly than before. We therefore undertook a critical evaluation of our own cases as well as of the reports of others for actual evidence of infections resulting from contact with patients. Although thousands of soldiers who contracted coccidioidomycosis in California during the war have returned to their home states, there has not been a single case of contact infection among them. Judging from the known incidence of benign residual pulmonary lesions and of disseminated lesions following primary coccidioidomycosis, there must be hundreds of men with chronic lesions in various parts of the country. Six patients with pulmonary cavities were actually followed by Bass and his colleagues in New York with the question of contagiousness in mind.[7] They found no evidence of infection, either obvious or inapparent, among the intimate contacts of these patients with known open cavities. Coccidioidin skin tests and chest roentgenograms of all the close relatives who were studied remained negative. In a large series of cases of chronic disease, including 92 of cavitation, seen over a period of more than ten years, Winn never saw evidence of transmission of the disease from one person to another, even when a mother remained at home with her children.[63] C. E. Smith has also not seen evidence of coccidioidomycosis among families of several patients with cavities.[5] Coccidioidin skin tests have remained negative after long contact between patients and families. Puckett, whose study of hyphae in cavities and granulomas concerned the first significantly large series, was also unaware of any evidence of contact infection.[10]

My experience agrees precisely with that of the above mentioned authors. Although there are always several patients with coccidioidomycosis on our wards, there has never yet been evidence of inter-human transmission of the disease, despite the fact that such patients are never isolated. The man in the bed next to that of a patient with coccidioidomycosis is very much safer than the transient farm laborer inhaling the dust of an endemic area.

It must be admitted that with the demonstration of hyphae in the sputum, transmission of coccidioidomycosis from a patient with a cavity becomes a possibility. I will even predict that someday an instance of man to man contagion will be reported, whereupon thousands of patients will be speedily and unnecessarily isolated. A realistic evaluation, however, shows the practical insignificance of the problem. The risk of contracting the disease from a patient is much less than the risk, however

slight of contracting it by driving through an endemic area An example of the former danger has yet to be reported examples of the latter are well known Yet as C E Smith observes *no one seriously proposes barring* travel through an endemic area [1] Neither does anyone suggest quarantining agricultural produce from southwestern states although rare examples of possible fomite transmission have been noted In my opinion ordinary hygienic precautions are all that is indicated in the care of patients with coccidioidal cavities If facial tissues are used for handkerchiefs discharges are promptly disposed of and linens are kept clean there should be small chance of propagation of mycelia and their airborne spores

This discussion of contagiousness concerns only pulmonary cavities and granulomas With possible rare exceptions mycelia have not been demonstrated in other forms of coccidioidal disease either primary or disseminated Even if the prediction of transmission from a patient with a cavity is someday realized that eventuality will have no implications regarding other types of the disease

The majority of the staff members of the Fresno Veterans Administration Hospital have only recently come to the San Joaquin Valley and are therefore not immune to coccidioidal disease The combined exposure of hospital personnel to infected patients including those with hyphae in the sputum now represents a total of several hundred exposure years Despite this theoretic hazard there was in five years of observation only one known case of primary coccidioidomycosis among the new members of the staff—that of a nurse who contracted the infection during the peak *of the coccidioidomycosis season just as any newcomer to this area might* do Her symptoms began about ten days after she made a pleasure trip outside of Fresno into adjacent parts of the San Joaquin Valley where the risk of infection is greater than in Fresno itself

In practice the risk of communicability of coccidioidomycosis is so slight that except for the ordinary precautions of decency it may be safely disregarded As far as primary coccidioidal pneumonia and disseminated coccidioidomycosis are concerned there is hardly even a theoretic hazard Even in the case of those with chronic coccidioidal cavitation of the lung clinical evidence is overwhelmingly convincing that coccidioidomycosis is not in the usual sense a contagious disease

*Chapter Six*

# Immunology of Coccidioidomycosis



## ACQUIRED IMMUNITY TO *COCCIDIOIDES IMMITIS*

THE PRESENCE of *Coccidioides immitis* in the body evokes a rapid and ordinarily effective immunologic response on the part of the host. Immunity thereby conferred is life long and complete. As far as we know, second attacks of coccidioidomycosis do not ordinarily occur, although there is evidence that unusually massive inhalation of spores may cause a partial break-through of immunity. Smith has reported the case of an immune laboratory worker who had mild malaise and recurrent precipitins after an overwhelming laboratory exposure.[8, 9] *There has been no analogous* situation following ordinary exposure. An analysis of alleged recurrent attacks of naturally acquired Valley Fever shows that what actually recurred was an undiagnosed illness accompanied by erythema nodosum. It has never been proved that two widely separate attacks of erythema nodosum were both coccidioidal. Furthermore, once immunity has been established, there is little danger of dissemination. If dissemination is going to occur, it almost certainly *does so during or soon* after the primary infection.

Several phenomena associated with the immunologic response of the body are measurable, providing precise diagnostic and prognostic tools. The immunologic methods of study are more accurate than those yet developed for most other fungus infections. They are the coccidioidin skin test, the precipitin test, and the complement fixation test.

## COCCIDIOIDIN SKIN SENSITIVITY

Coccidioidin is the filtrate of liquid cultures of *Coccidioides immitis* When used intelligently it is the most valuable single tool generally available for the diagnosis of coccidioidal infections

Coccidioidin has been prepared in various ways Cooke who in 1915 made the first attempt to study cases of coccidioidomycosis serologically tried skin testing with emulsions of mycelia and spherules [4] His results were equivocal Davis in 1924 prepared the first successful coccidioidin a suspension of the fungus rather than a filtrate [6] Hirsch and his co workers in 1927 used the first broth filtrates for skin testing [7, 50] A year later Jacobson skin tested patients with progressive coccidioidomycosis using a filtrate of Sabouraud s broth and then glucose broth [93] The first skin testing survey was accomplished by Hurwitz Young and Eddie in 1938 using a broth filtrate which had been killed by heat dried and suspended in phenolized saline [13] Kessel s veal broth culture [53] heat killed and ground with sand was the coccidioidin used by Gifford in her classic study of Valley Fever [31] In 1943 Hassid Baker and McCready[349] isolated from coccidioidin an immunologically active polysaccharide consisting of galacturonic acid glucose and an unidentified sugar in the approximate ratio of 1 to 6 to 3

The coccidiodin most widely used at the present time was developed by C E Smith after he had tried and discarded a number of other preparations because of their content of foreign protein or the prohibitively long time required for their manufacture [1, 4] For culture he modified and adapted the asparagine formula already proved satisfactory in the preparation of the tuberculin of "Purified Protein Derivative" For the inoculum he uses ten strains of *Coccidioides immitis* isolated variously from patients with disseminated infections and poor sensitivity with erythema nodosum and strong sensitivity with pleural effusion with uncomplicated primary infections and with residual pulmonary cavitation Diverse endemic areas are represented Incidentally Smith was able to demonstrate no significant differences in the coccidioidin produced by various strains He also showed that grinding the mycelial mat prior to filtration brought about no increase in the amount of coccidioidin produced

The fungus is grown for six to ten weeks the time period being determined by potency tests Aqueous merthiolate is added and the material is passed through a Berkefeld filter Tests for sterility potency and specificity are then made The standard dilution for routine testing is 1 100

Coccidioidin is a stable substance being only slightly attenuated by heating in an autoclave at 250 F for ten minutes or in live steam for an hour Undiluted it may be kept at room temperature without loss of potency for at least ten years and perhaps indefinitely Even when diluted

it maintains its strength for several years at room temperature unless it has been contaminated in which case it may cause either false negatives or false positives

The coccidioidin skin test is given in the same way as the tuberculin test The luer must never have been used for any other biological preparation notably tuberculin 0 1 ml of the appropriate dilution (usually 1 100) is injected intradermally A positive reaction is an induration 5 mm or more in diameter Usually there is also erythema but sometimes the blush is so faintly pink that it is not noticed so that the test may be erroneously called negative even though there is detectable induration or edema

Sources of error in administration and interpretation are (1) using contaminated coccidioidin preparations (2) using luers previously used for tuberculin testing (3) injecting subcutaneously instead of intracutaneously (4) reading too early or too late and (5) overlooking induration because erythema is faint or absent

In the skin of a sensitive person coccidioidin causes the delayed type of reaction Occasionally an immediate reaction is seen like that caused by intradermal pollen injections in a person with pollinosis with erythema wheal and pseudopods appearing in 15 to 60 minutes and fading in a few hours Such a reaction is not necessarily indicative of coccidioidin sensitivity for it can occur in patients who have never been in an endemic area and who do not later show the specific delayed reaction

The diagnostically significant reaction an induration at least 5 mm in diameter with or without erythema begins within 6 to 24 hours Maximal reaction appears in an average of 36 hours The test should be read at both 24 and 48 hours If read only at 24 hours slow reactions may not yet have appeared whereas if read only at 48 hours a few may already have vanished Occasionally a reaction may not be visible for three days or maximal for four days The significance of the unusually delayed reaction is the same as that of the typical 24 48 hour reaction

Coccidioidin sensitivity is not passively transferred to the skin of a non reactor by intradermal injection of serum from a patient with high sensitivity Furthermore repeated skin testing with coccidioidin does not induce skin sensitivity or stimulate the formation of humoral antibodies

Sensitivity to coccidioidin usually does not appear until several days after the onset of symptoms of primary coccidioidomycosis If tested too early the specific reaction will not yet have appeared and if the test is not repeated the diagnosis will be overlooked It is nevertheless desirable to test immediately for an early negative reaction is the best possible background for evaluating a later positive reaction Coccidioidin sensi

tivity measured by a 1 100 dilution usually appears in two days to three weeks after the first symptoms or nine days to six weeks after exposure If 1 1 000 coccidioidin is used sensitivity may not be apparent until two or three weeks later Rarely sensitivity does not appear for six weeks At the other extreme conversion of the skin test from negative to positive has been noted five days before the onset of symptoms of a moderately severe primary infection If the illness is coccidioidal sensitivity invariably appears sometime during the primary stage and increases for several weeks except in certain cases of overwhelming dissemination A patient with a mild reaction during the first week may have a severe reaction two weeks later

Erythema nodosum itself a manifestation of hypersensitivity is accompanied by strong dermal reactions to coccidioidin so that it is prudent to use higher dilutions than usual (1 1 000 or 1 10 000) in testing a patient so afflicted Skin testing during primary coccidioidomycosis sometimes precipitates erythema nodosum or causes its recurrence Inasmuch as both are expressions of the same sensitivity erythema nodosum does not appear before reactivity to coccidioidin A negative coccidioidin reaction in the presence of erythema nodosum therefore rules out coccidioidomycosis as the cause Although coccidioidin skin testing occasionally flares up erythema nodosum the reaction is more annoying than serious Healing of the pulmonary lesion is not thereby delayed nor is convalescence prolonged Furthermore coccidioidin administration never causes dissemination nor does it reactivate an old quiescent infection

Coccidioidin sensitivity after infection is generally of long duration although it may wane slowly It has been demonstrated as long as 21 years after a primary infection In highly endemic areas 80 to 90 per cent of long term residents react so that sensitivity must ordinarily be a stubborn characteristic Although persistent sensitivity has been blamed on repeated exposure it has been known to remain for over 20 years after the last possible contact with the fungus Rapid loss of sensitivity within a few months after convalescence has been described in small series but those with the widest experience have observed that more long lasting reactivity at least for a number of years is the rule When sensitivity does tend to decrease it may do so even in the face of constant exposure to high concentrations of the fungus It has been shown that coccidioidin reactors may harbor spherules of *Coccidioides* in ancient calcified coccidioidal lesions providing an explanation for their persistent sensitivity Like a positive reaction to tuberculin a reaction to coccidioidin does not indicate when infection has occurred It tells what" not when" Unless conversion from negative to positive is noted the time of the infection cannot be inferred from the skin test alone

There are two situations in which an active coccidioidal infection may not be reflected by a positive skin test (1) early in the course of the *primary disease before sensitivity* has appeared and (2) in the stage of dissemination When dissemination occurs skin reactivity may decrease or disappear About 70 per cent of such patients will not react to a 1 100 dilution about 40 per cent will not react even to a 1 10 dilution Nevertheless although it is a fallible diagnostic tool coccidioidin is valuable prognostically High sensitivity does not prevent dissemination but maintained sensitivity augurs a better chance of survival Except in cases of meningitis three quarters *of those who continue to react to a 1 100 di*lution will survive but only a sixth of those reacting negatively Meningitis although invariably fatal is often associated with strong cutaneous reactivity unless it is part of a generalized miliary dissemination in which case there is usually anergy

*The loss of cutaneous sensitivity may not be specific for coccidioidin* for cases have been reported in which sensitivity to tuberculin was also lost as miliary dissemination of the coccidioidal lesion occurred Recovery from progressive coccidioidal granuloma is often accompanied by re establishment of sensitivity to coccidioidin

Skin sensitivity is sometimes lost with residual pulmonary lesions (cavity or granuloma) and humoral antibodies are usually low or absent in this form of the disease

Although there is no cross sensitivity between coccidioidin and tuberculin there are cross reactions with the antigens of several other related fungi This problem became apparent with Emmons s discovery of *Haplosporangium parvum* in Arizona and the cross reaction between *coccidioidin* and haplosporangin

Early in World War II Smith noticed that a large number of soldiers from central United States reacted to coccidioidin[316] He inferred that another fungus such as *Histoplasma capsulatum* might be responsible for the cross reaction and postulated a *benign form of histoplasmosis* which *might* have caused the hitherto unexplained pulmonary calcifications among residents of that area His conjecture was proved correct by the investigations of Christie and Peterson[31] and Palmer[46] Smith then demonstrated that a primary histoplasmin sensitivity was responsible for the low grade reactions to coccidioidin among residents of the Ohio and Mississippi Valleys Coccidioidin skin testing surveys in Central America have also resulted in a small percentage of positive reactions (Table X) Histoplasmosis now known to exist there is probably responsible for the false positives as it was in the army surveys

There is also cross sensitivity between coccidioidin and extracts of *Blastomyces* species North American workers have shown cross reactions with blastomycin from *Blastomyces dermatitidis* and South Ameri

can investigators have reported similar results with paracoccidioidin[11] from *Blastomyces brasiliensis* (formerly *Paracoccidioides brasiliensis*) the causative agent of South American Blastomycosis or paracoccidioidomycosis

Cross reaction is usually faint or absent when normal dilutions of these antigens are used but it may be apparent with higher concentrations such as 1 10

## SEROLOGICAL REACTIONS TO COCCIDIOIDAL INFECTION

Prior to 1937 serologic studies of patients with coccidioidomycosis were more a curiosity than a recognized necessity In the only known form of the disease progressive coccidioidal granuloma diagnosis was made by demonstration of *Coccidioides* in the lesions either by culture or biopsy so that serologic confirmation was not important Today however with the recognition of the vastly wider spectrum of coccidioidal infection serologic tests are necessary both for diagnosis and prognosis

Although other methods of diagnosis—i e recovering the fungus from the sputum—are theoretically superior in actual experience the serologic tests are more practicable Sputum may be scanty and its culture may be hazardous particularly if the presence of *Coccidioides immitis* is not suspected and precautions are not taken Unless there has been an earlier negative reaction a positive coccidioidin skin test is suggestive but not conclusive Because of the drawbacks of these other methods serologic tests have recently come into their own

Cooke who in 1914 was the first to study the immunology of coccidioidomycosis demonstrated a specific precipitin reaction by the ring method but could not show complement fixation or skin sensitivity[4] Davis who made the first useful coccidioidin also demonstrated complement fixation using as his antigen a 4 week old culture which had been ground up[6]

C E Smith developed on a wide scale the modern techniques of serologic study Although his investigations were well under way in 1940 he did not finally publish his results until 1950 when he had already performed over 21 000 simultaneous precipitin and complement fixation tests[5 6 9 7]

Coccidioidin i e the filtrate of cultures of *Coccidioides immitis* is the antigen for both the precipitin and complement fixation tests The preparation of coccidioidin has been described above For serologic testing as for skin testing multiple strains of *Coccidioides immitis* are used in the manufacture of coccidioidin although there has been no evidence of antigenic variation even among strains from different continents Each lot of coccidioidin must be separately standardized The antigens are almost indefinitely stable at room temperature holding their potency for

Precipitins are specific immune bodies which react directly with antigens to produce a precipitate. To detect the specific precipitin for *Coccidioides immitis* 0.2 ml of undiluted serum is placed in each of several tubes. Coccidioidin is then added—0.2 ml undiluted to the first, 0.2 ml of 1:10 dilution to the second, and 0.2 ml of 1:40 dilution to the third. A control is run using uninoculated asparagine medium instead of coccidioidin. Precipitins are demonstrated by the formation of a button or flake after the mixed components have stood for a while. Daily readings are made for 5 days. Button formation is recorded as ++++.

The precipitin and complement fixation tests are highly specific for coccidioidal disease. Cross reactions have not been noted with bacterial, rickettsial, and viral infections. Furthermore, several mycoses—such as actinomycosis, blastomycosis, and cryptococcosis—have so far not shown non-specific reactions to the coccidioidal antigen. The exception is histoplasmosis, in which coccidioidin may weakly fix complement both in the acute disease and in some cases of the disseminated form. The titers are usually low, e.g., 1:16, compared with the histoplasmin titer, which may be 1:128 or higher. In blastomycosis coccidioidin does not fix complement, but blastomycin may give high complement fixation titers in coccidioidomycosis.[7, 8]

Bieberdorf and Chamblis have described a serum for use as a positive control in areas where positive sera are not easily obtained. Their method involved using the sera of rabbits infected artificially.[63]

The serologic patterns in various types of coccidioidomycosis are sufficiently specific to be of great diagnostic and prognostic aid. Fortunately, precipitins and complement-fixing antibodies appear at different times and under different circumstances, so that the information derived from each is distinctive. In brief, immunologic characteristics of primary coccidioidal infection may be summarized thus:

(1) Coccidioidin skin sensitivity is present in every case of primary coccidioidomycosis—whether inapparent, moderate, or severe—and usually persists for years unless overwhelming dissemination occurs.

(2) Precipitins appear next, are present in most symptomatic primary infections, and usually persist for only a few days or weeks, even when dissemination follows.

(3) Complement-fixing antibodies appear last and then only in more severe infections, persist for several months or even years in uncomplicated disease, and ordinarily rise very high in dissemination and persist throughout the period of generalized disease.

In primary coccidioidomycosis one or both serological tests are positive in about 90 per cent of patients with symptomatic disease, but only

in 10 per cent or less of persons with inapparent infection In general the more severe the infection the more likely the development of humoral antibodies The precipitin reaction is positive in about three fourths of the cases of uncomplicated symptomatic primary coccidioidomycosis nearly half the time the precipitin test alone is positive About a third have both precipitins and complement fixing antibodies In only a few (less than a fifth) is the complement fixing test alone positive

If both serologic tests are negative throughout the course of a moderately severe pulmonary infection of unknown cause there is only about one chance in ten that it is coccidioidal If tested on only one occasion the presence of antibodies may be missed

Humoral antibodies are always preceded by cutaneous sensitivity In the uncomplicated primary infection it is therefore fruitless to do serologic tests until the skin is positive The skin test becomes positive during the first week in over 80 per cent of infections by the end of the second week in over 90 per cent by the end of the third week in virtually 100 per cent

Precipitins lag somewhat behind skin sensitivity They appear in about 50 per cent of symptomatic cases during the first week in 85 per cent by the end of the second week and in about 90 per cent by the end of the third week Almost none make their initial appearance thereafter By the fourth week precipitins begin to disappear the percentage of positive reactions falls steadily to almost zero in 3 or 4 months In all of Smith s nearly forty thousand tests precipitins persisted longer than seven months after uncomplicated primary infections in only a handful[6,7] Four patients still had demonstrable precipitins at 7 to 9 months three at 10 to 12 months one in the second year and one in the third year Almost as rarely were disseminated infections accompanied by persisting precipitins—eight in the second year three in the fourth year and one in the ninth year Once they have vanished precipitins reappear in only one situation—when rupture of a residual pulmonary cavity causes coccidioidal hydropneumothorax

Complement fixing antibodies develop more slowly than precipitins In less than a tenth of symptomatic cases do antibodies appear during the first week but they continue to appear for three months whereas new precipitins do not appear after the first month In uncomplicated primary infections complement fixing antibodies usually regress during the first year most often during the first six or eight months Only rarely do they disappear before precipitins do In the presence of benign residual pulmonary lesions complement fixation may persist at a low level for several years When dissemination occurs a high titer usually persists until death or until healing of the disease I have seen a maximal titer twenty years after the first symptoms of a peripheral granuloma

Chapter Seven

# Variations in Susceptibility to Coccidioidal Infection

Racial Differences
Sex Differences
Age Differences

## RACIAL DIFFERENCES

It was noticed very early in the Twentieth Century that members of the dark skinned races are particularly susceptible to disseminated coccidioidomycosis Part of this predeliction was at first thought to be explained by the fact that as farm laborers they were more often exposed to infectious dust but it is now obvious that racial differences are real and striking

There is no particular difference in the racial susceptibility to *primary* coccidioidomycosis for persons of no one race are more likely to inhale the spores than those of another Coccidioidin skin testing surveys show essentially the same general patterns in different races It is in the *reaction* to the primary infection that racial differences are so great Negroes and Filipinos are much more prone than Caucasians to have severe primary illnesses and to suffer dissemination To be specific coccidioidomycosis is more than ten times as likely to become disseminated in the Negro than in the Caucasian In the Filipino the hazard is even higher

The relative racial susceptibility to coccidioidal granuloma has been estimated from morbidity data gathered in Kern County by Gifford who calculated case and death rates per 100 000 for the years 1901 1936 [39] Enough cases had occurred in four groups—Caucasian Mexican Negro and Filipino—to give valid data From Table VI it may be seen that Mexicans are about three times Negroes 14 times and Filipinos 175 times as prone to suffer disseminated coccidioidomycosis as Caucasians The total number of cases in other racial groups was small but it appears that

there is also increased susceptibility in American Indians, Japanese and Chinese.

Gifford also noted in 1937 that Caucasians, with 67 per cent of the total population in Kern County, contributed only 41 per cent of the cases of coccidioidal granuloma, whereas other races, with only 13 per cent of the total population, contributed 59 per cent of the cases. Over 22 per cent of the cases occurred in Filipinos alone, although they represented only 0.25 per cent of the population.

TABLE VI

DISSEMINATED COCCIDIOIDOMYCOSIS: COMPARATIVE MORBIDITY AND MORTALITY RATES AMONG VARIOUS RACIAL GROUPS IN KERN COUNTY, CALIFORNIA, 1901-1936

| *Race* | *Case Rate per 100,000* | *Case Rate Ratio* | *Death Rate per 100,000* | *Death Rate Ratio* |
|---|---|---|---|---|
| Caucasian | 82 | 1 | 28 | 1 |
| Mexican | 281 | 3.4 | 140 | 5 |
| Negro | 1,122 | 13.7 | 654 | 23.4 |
| Filipino | 14,350 | 175 | 5,381 | 192 |

Adapted from data of Gifford, Buss and Douds.[23] By permission.

The reason for the difference in racial susceptibility is unknown. In the case of certain other diseases in which there is a similar racial difference, it has been proposed that long exposure has brought about a racial resistance. This can hardly be true of coccidioidomycosis, for it is a new disease to Caucasians as well as to Negroes and Filipinos. Indeed the only group which could have had long exposure—the California Indians—have somewhat less resistance than Caucasians, if Gifford's figures are representative.

For some reason other than long ancestral exposure, members of the white race have the ability to develop higher immunity to coccidioidomycosis than other races. Associated with this better immunity is the higher incidence of classical Valley Fever among Caucasians. Although erythema nodosum occasionally occurs among Negroes and Filipinos, the incidence is lower than among Caucasians. It is more likely to occur among Negroes of mixed ancestry than in pure blooded Negroes.

The question sometimes arises concerning differences within the white race. A definite answer cannot be given. There are no figures, for instance, to compare the incidence among those of Nordic and those of Latin descent. The number of Portuguese among the first victims of coccidioidal granuloma in California is suggestive of increased susceptibility, but precise data are lacking.

## SEX DIFFERENCES

It was originally thought that coccidioidal granuloma was a disease of adult males Only two of the first 60 cases reported in California involved females When Riesman and Ahlfeldt made their study of 87 cases in 1927 a main point of their paper was that occasionally the disease does occur in women and children [4]

Now it is known that there is no sex predeliction in primary coccidioidal infection Skin testing surveys have shown equal distribution of positive reactions between the sexes There are nevertheless differences in the reaction to primary infections Typical Valley Fever i e primary coccidioidomycosis with erythema nodosum is much more common in women than in men In fact primary coccidioidomycosis is more often diagnosed in women simply because the skin lesion converts an inapparent infection into one which is very obvious Erythema nodosum occurs in about 5 per cent of all infections in men and about 25 per cent in women Before puberty this sex predeliction for skin manifestations is not apparent but thereafter the trend is clear

Males on the other hand are much more prone to suffer dissemination of the infection In Gifford's review of coccidioidal granuloma in Kern County the case rate per 100 000 for men was 265 and for women only 74 or nearly 4 to 1 [11] In Beck's earlier survey the ratio was nearly 6 to 1 [131] The early figures may have been weighted by the fact that there was a preponderance of dark skinned males brought into the valley for agricultural work but it is still true that the infection is less likely to become disseminated in women than in men An exception to this rule is noted late in pregnancy when the female susceptibility to dissemination increases [6, 6]

## AGE DIFFERENCES

By itself age has no effect on the incidence of primary coccidioidomycosis In skin testing surveys it is of importance only in so far as it affects the length of residence in endemic areas Numerous investigations in endemic areas show increasing percentages of positive reactions with the age of children

Age probably has no clear cut influence on susceptibility to dissemination Faber felt that children under the age of four years were somewhat more susceptible than older children and adults [93] Townsend and McKey reporting a case of fulminating dissemination in a 3 week old infant proposed that the newborn has very little resistance to coccidioidal disease [7, 8] Granting that such grave illness can occur in the infant however it seems statistically no more frequent than at other ages Considering the large number of children born in highly endemic areas it would be expected that serious infections would occur now and then

*Chapter Eight*

# Pathology and Pathogenesis of Coccidioidomycosis



## EARLY PATHOLOGIC STUDIES OF COCCIDIOIDOMYCOSIS

THE ONLY unique feature of the coccidioidal lesion is the presence therein of the spherule of *Coccidioides immitis*. The pathologic appearances are not otherwise distinctively different from those of a score of other diseases ranging from syphilis to sarcoid.

Coccidioidomycosis is often compared to tuberculosis. There are clinical, *immunologic* and *roentgenologic similarities*, but the pathologic mimicry is the most striking of all.[104] The characteristic feature of both is the tubercle, but the resemblance extends also to the exudative pulmonary lesions, the cold abscesses of soft tissues, and the verrucous lesions of the skin.

The similarity of coccidioidal and tuberculous lesions was noted by Rixford in the first brief note concerning his original North American case of coccidioidomycosis. Later in his paper with Gilchrist in *1896* he remarked that "Both to the naked eye and microscopically, the nodules were indistinguishable from tubercles save that they contained the protozoan organisms and did not contain tubercle bacilli."[8]

It was Ophuls who made the definitive description of the pathological anatomy and histology of coccidioidomycosis in two classic studies pub-

lished in 1905 [1] In the closing sentence of one of them he wrote "The resemblance of the disease to tuberculosis is so great clinically and anatomically that the true nature of the process is recognized only when a careful microscopic examination is made of the diseased tissues or the pus in the lesions" [1] He noted the great variety of lesions produced by the parasite and the various organs affected As in other infectious granulomas he wrote there are several types of lesions the most characteristic being the nodule of granulomatous tissue In addition there are suppurative lesions both acute and chronic and caseation He demonstrated tubercles with giant cells of the Langhans type submiliary abscesses surrounded by thick layers of epithelioid cells and acute abscesses filled with polymorphonuclear leukocytes

Ophuls thought that he could distinguish between the type of lesions produced by spherules of various degrees of maturity "We observe in this disease" he wrote "remarkable transitional stages between nodular lesions on one hand and chronic miliary abscesses on the other There are nodules with central abscess formation and chronic abscesses with central caseation of their contents Furthermore sometimes we find large masses of fibrous tissue with numerous very large fibroblasts few leucocytes and occasional giant cells usually including one or more of the parasites It may appear extraordinary that one parasite should be able to produce lesions of such entirely different aspect A careful study of the tissues however has convinced me that these differences are largely dependent on the stage of development in which the parasite is present The adult forms are found in the less acute lesions whereas the abscesses always contain sporulating forms often in very large numbers It seems then that only after the bursting of the capsule the substances which produce the suppurative process gain access to the tissues"

## PATHOLOGY AND PATHOGENESIS OF PRIMARY COCCIDIOIDOMYCOSIS

Because men do not die of uncomplicated primary coccidioidomycosis its pathologic picture in human beings has not been adequately studied From analogies to the disease in experimental animals and from a synthesis of certain observations in man the pathogenesis may be satisfactorily postulated

When contaminated air is inhaled arthrospores and chlamydospores are deposited on the tracheobronchial mucosa and the membrane lining the alveoli and alveolar ducts The tiny dimensions of the spores—2 to 10 micra—allow them to traverse the smallest passages The metamorphosis from hyphal spore to tissue sporangium presumably follows the same pattern in the lung that it does in the tissues of experimental animals as

described in Chapter Three In 4 to 7 days mature *spherules develop* from mycelial spores

The initial lesions would be expected in the bronchial mucosa as well as in pulmonary parenchyma Faber Smith and Dickson inferred from the ease with which spherules are found in the sputum that bronchial lesions are frequently present [8] Bronchoscopic observations of Birsner and Cotton have confirmed the existence of a primary bronchitis even in cases in which pneumonitis is not clinically evident [41] They concluded that pulmonary coccidioidomycosis is primarily an endobronchial disease

Observations in experimental and domestic animals have elucidated the pathology of the early pulmonary lesion By means of an ingenious apparatus Cronkite and Lack administered spore bearing air to the nostrils of guinea pigs without trauma and without contamination of the rest of the animals body Between 8 and 21 days after exposure the lungs contained barely visible translucent grey nodules similar to tubercles which microscopically were typical granulomas In the earliest lesions there was merely thickening of the alveolar septa because of the infiltration of mononuclear cells and occasional eosinophiles As the lesion expanded the alveoli were obliterated and normal architecture was replaced by the epithelioid cells and giant cells of the tubercle Granulomas were soon present in the tracheobronchial lymph nodes as well as in the lung itself

Similar lesions of the lungs and lymph nodes have been seen in slaughtered cattle and in trapped rodents It is presumed that such lesions also develop during the primary stage of human coccidioidomycosis In mild and asymptomatic cases lesions may be few and limited In more severe cases an exudative reaction also occurs in the lung In uncomplicated disease lesions may be completely resorbed or may be enclosed in a fibrous capsule

Autopsy studies of patients who die soon after the primary disease give an idea of the pathological processes during the primary phase [4] The mildest lesions may be a lobular focal pulmonary consolidation resembling any bacterial pneumonia Alveoli are filled with an exudate which contains spherules polymorphonuclear leukocytes and a few mononuclear cells Little fibrin is present in such an exudate so that resolution may be complete In more severe lesions consolidation may be extensive and even lobar with great suppuration hemorrhage necrosis granuloma formation or fibrin production Such lesions could heal only with considerable hyalinization and fibrosis In addition to pulmonary lesions there may be necrotizing ulcerative bronchitis bronchiolitis and bronchiectasis Regional hilar and mediastinal lymph nodes are enlarged and contain suppurative and granulomatous lesions Inasmuch as these are autopsy findings they may not be characteristic of the usual mild infection Never

theless they probably indicate the type of pathologic process which follows invasion by *Coccidioides immitis*

***Histopathology of the Tubercle or Granuloma*** Tuberculoid lesions appear not only in tuberculosis but also in coccidioidomycosis leprosy syphilis typhoid fever lymphogranuloma inguinale tularemia brucellosis torulosis schistosomiasis sarcoidosis beryllosis sporotrichosis and other diseases The presence of the causative agent of these diseases calls forth an infiltration of mononuclear cells—variously called macrophages histiocytes and reticuloendothelial cells

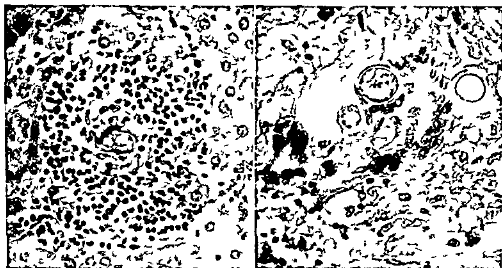


Figure 19 Coccidioidal tubercle and spherule containing giant cell human lung (From Winn Coccidioidomycosis in Hinshaw and Garland *Diseases of the Chest* Philadelphia and London W B Saunders Company 1956 )

The epithelioid cell—as the mononuclear cell is called because of the changes occasioned by the encounter—is a large pale cell with rather vague margins a large vesicular nucleus and abundant cytoplasm Amitotic nuclear division or fusion of epithelioid cells produces giant cells Usually their many nuclei are radially arranged in a rosette about the periphery—the Langhans cell Sometimes nuclei are scattered haphazardly throughout the cytoplasm—the so called foreign body giant cell Giant cells said not to appear until necrosis or caseation has taken place are located in the middle of the caseous area if it is small or at the edge if it is large It is thought that the function of giant cells is to digest and remove dead tissue When caseation or coagulation necrosis occurs epithelioid cells lose their outline their nuclei disappear, and their structure fades

Around the epithelioid and giant cells there appears a zone of lymphocytes and plasma cells This whole mass of cells constitutes the tiny translucent nodule or tubercle Stained with hematoxylin and eosin the homogeneous necrotic center is red the peripheral giant cells and epithelioid cells are pale and in the outer zone the lymphocyte nuclei stain dark blue

## PATHOLOGY AND PATHOGENESIS OF DISSEMINATED COCCIDIOIDOMYCOSIS

Primary coccidioidomycosis is an air borne infection the lesion is a bronchitis bronchiolitis or bronchopneumonia Secondary coccidioidomycosis is blood or lymph borne the lesion can be any combination of suppuration necrosis and granuloma in almost any organ

Forbus and Bestebreurtje [407] pursuing the reasoning of Ophuls have further correlated the various forms of the parasite with different types of lesions They postulate that each form of *Coccidioides*—chlamydospore spherule or endospore—has its own peculiar chemotactic properties Because chlamydospores or arthrospores are present so transiently at the initiation of the primary infection they cannot be studied pathologically in human tissues Only by analogy to experimental infections can their effect be inferred Presumably the reaction of tissues to hyphal spores is similar to the reaction to endospores

When endospores are liberated from the mature spherule an intense polymorphonuclear reaction is evoked Neutrophiles rush to the endosporulating organism invade the ruptured capsule and attempt—usually without success—to phagocytize the spores The organism on the other hand is highly destructive of the inflammatory cells which soon show evidence of injury and eventually die leaving great masses of cellular debris Blood vessels are likewise damaged and bloody fluid escapes into the diseased tissues Widespread necrosis or liquefaction occurs

When the endospore has become a spherule with a well informed capsule *the polymorphonuclear leukocytes are replaced by large mononuclear* cells which often engulf the maturing parasite In this intermediate stage the organism may cause little necrosis and may in fact stimulate proliferation of the host tissues Mononuclear cells in contact with the spherule begin to grow reproduce and develop nuclei eventually forming large giant cells Surrounding mononuclear cells also proliferate bringing about the typical epithelioid reaction Rupture of the mature spherule and liberation of its endospores cause destruction of the engulfing mononuclear cell and dispersion of the new generation of parasites into nearby tissues The cycle begins again with the polymorphonuclear reaction

The balance between suppurative and mature granulomatous reactions determines the outcome. If tissue resistance is good, granulation is followed by hyalinization, scarring, and occasionally by calcification. If resistance is poor, suppuration may become predominant. Primary pulmonary lesions are preponderantly granulomatous; disseminated lesions tend to be suppurative.

## THE VARIETIES OF COCCIDIOIDAL LESIONS IN DIFFERENT ORGAN SYSTEMS

### Skin and Subcutaneous Tissues

Sooner or later the skin is involved in almost all cases of disseminated coccidioidomycosis except meningitis. Historically, the first cases of coccidioidal granuloma came to medical attention because of the skin lesions. Many of the important studies of progressive coccidioidomycosis have been made by dermatologists. Sometimes a skin lesion, obviously secondary, is even yet the occasion of a dermatologic paper on "Primary Cutaneous Coccidioidomycosis." [1]

The most characteristic type of lesion is the verrucous granuloma similar to that seen in blastomycosis. When several such lesions appear in crops they generally indicate acute miliary dissemination (Fig 20), but solitary nodules may appear in chronic, less malignant disease. The verrucous skin lesion usually is seen first on the face or scalp, although it may occur anywhere. A characteristic site is the nasolabial fold. It begins as an epidermal thickening without much redness or inflammation. When larger it looks much like a common wart, although it is darker. The surface of the lesion has tiny papilliform excrescences from which a drop of serum may sometimes be expressed. A crust may form, obscuring the warty characteristics. In chronic coccidioidal disease the lesion may persist for months no larger than a small pea. At other times it may grow to many centimeters in diameter, resembling a fungating epithelioma. It may eventually heal, leaving an atrophic scar, or it may persist for several years without evidence of progression. Sometimes, as in the original cases of both Posadas and Rixford, it may slowly spread until death ensues with widely disseminated lesions. In fulminating coccidioidomycosis the lesions may enlarge, become pustular, and coalesce, destroying all human semblance.

At times the lesion seems to follow a local injury. Usually the relationship is chronological rather than causal, but occasionally it may be real.

Another sort of lesion is the subcutaneous abscess. In miliary disease the body may be covered with lesions a few millimeters in diameter. In chronic infection there may be one or two large abscesses, commonly on



Figure 20 Verrucous skin lesions in fulminating disseminated coccidioidomycosis in in a 30 year-old Filipino vineyard laborer fatal in five weeks (From Winn *Annals of Internal Medicine* 17 407-422 1942 )

A



B







C D

Figure 21 A Severe coccidioidal pneumonia occurring in a Filipino farm laborer B C and D Four months later osteolytic coccidioidal lesions of the bones of the skull hand and foot

**Liver**

Like the spleen the liver is frequently subject to (1) enlargement due to general toxicity and (2) miliary granulomas and abscesses

**Bones**

Coccidioidal osteomyelitis occurs in about half of the cases of disseminated coccidioidomycosis Only cutaneous lesions are more characteristic Practically all bones in the body have been infected and usually the process is multifocal involving several bones at once (Fig 21) Bones most commonly diseased are the ribs vertebra skull and bones of the extremities particularly the distal portions In flat bones lesions are prone to occur in the middle In long bones they are more likely to be located in the ends particularly near bony prominences such as the ankle or tibial tubercle Coccidioidal osteomyelitis is primarily an osteolytic proc



Figure 22 Coccidioidal dactylitis in a 6 month old child (From Cohen *Archives of Pediatrics* 66 241 265 June 1949 )

ess although in chronic infections there is later a strong osteoblastic tendency, sometimes with complete healing Soft tissue abscesses do not ordinarily *cause lesions of underlying bone* but bony lesions often produce soft tissue abscesses and ulceration Lesions in epiphyses may perforate the articular cartilages and penetrate joints Inward extension of skull lesions may involve the meninges with the usual lethal *termination* Infection in the lumbar vertebra may extend through the attachments of the psoas muscle producing a psoas abscess like that of tuberculosis Lesions originating in the ribs often dissect widely before erupting through the skin

If multifocal coccidioidal osteomyelitis is part of widespread systemic dissemination the prognosis is poor If however, the process is limited to one or several bones it may be a chronic non progressive self limited disease Birsner and Smart have emphasized the essentially benign nature of chronic osseous coccidioidomycosis when no other tissues are involved[891] In a report upon 18 cases of 4 to 29 years duration they described healing and return to full activity in most One patient s lesions of the facial bones right wrist left calcaneous pelvis and right scapula healed in five years and *did not recur in the next 24 years Apparent cure is often* achieved by amputation of diseased extremities as in the case of a white infant cited by several authors [1, 893] who was born during a dust storm and suffered a respiratory infection at two weeks of age and a dactylitis at four weeks (Fig 22) The diseased finger was amputated six months later She was well and had a minimal complement fixation titer at the age of seven years

## Joints

The transient arthritis accompanying primary pulmonary coccidioidomycosis has already been described "Desert rheumatism" occurs in 2 to 5 per cent of all cases in the initial stage often in association with erythema nodosum Joints may be painful tender swollen and red as they are in rheumatic fever Arthritis at this stage is a sensitivity *phenomenon* and like erythema nodosum indicates a good immunity The fungus is not present in the joints and no permanent damage is done

*The situation is quite different in secondary* coccidioidomycosis Joints are also frequently involved in the generalized infection but the lesion is no longer due merely to sensitivity but to actual invasion of the *joint* by the fungus Coccidioidal arthritis has been noted in about a third of the cases of chronic dissemination The ankle is most often involved followed in frequency by the knee foot elbow wrist shoulder and hand Occasionally the vertebral joints and hip are involved The arthritis is often multiple

At first affected joints are acutely swollen and red Later fluctuation may take place burrowing to the overlying skin with the formation of discharging sinuses Sometimes disseminated lesions appear first in the synovial membrane More often the joint is involved by extension from an adjacent focus of coccidioidal osteomyelitis Roentgenographic studies show destruction of articular cartilages narrowing of joint spaces and absorption of bone with little tendency to heal

Diseased joints contain purulent or caseous material and the tissues contain granulomatous lesions with spherules of *Coccidioides* Coccidioidal arthritis closely resembles that of tuberculosis

Sotelo-Ortiz has described two cases of coccidioidal synovitis of the knee in which there were pain swelling and limited motion for several years[8] Synovectomy lessened the symptoms The excised synovial membranes were greatly thickened characteristic of chronic villous synovitis

## Skeletal Muscles

Although striated muscles are uncommonly the primary sites of blood borne disseminations they are often involved in the extension of infections from osseous lesions As in tuberculosis psoas abscesses are now and then seen

## Lungs Bronchi, and Pleura

The lungs and pulmonary tree are doubly vulnerable to coccidioidal infection They are open to the air borne spores which cause primary bronchitis and bronchopneumonia they are also susceptible to the same processes which cause disseminated lesions in other organs Sometimes secondary spread occurs via the bronchi themselves as when a necrotic lymph node erodes and discharges into a bronchus At other times particularly during the course of a fulminating infection the organisms are widely disseminated via the pulmonary circulation causing miliary abscesses and nodules throughout the lungs (Fig 23) Sometimes hematogenous spread into a lung where coccidioidal activity has long been quiescent marks the terminal phase of extra pulmonary dissemination

Pleural reaction to coccidioidal disease varies from a fibrinous inflammatory reaction to severe granulomatous thickening interspersed with abscesses or empyema Sometimes there is pleural effusion which even in non disseminated infections may contain the fungus Abscesses in the ribs are sometimes accompanied by secondary pleural lesions

## Adrenals

In the report of the first autopsy done on a victim of coccidioidomycosis Rixford and Gilchrist noted that the adrenals were "enormously en

larged and were filled with irregular yellowish masses" scrapin
which showed an enormous number of protozoa." Forbus and B
breurtje noted granulomatous lesions in the adrenal glands of 16 of
50 cases studied at autopsy but they had no record of clinical ad
insufficiency in any of their series.[48] Despite the frequency of ad
localization Addison's disease has been reported on only rare occa
in progressive coccidioidal disease. Maloney has described two



Figure 23. Section of the lung of a 21 day old infant dying of acute disseminated co-*ccidioidomycosis* showing the cut surface thickly studded with necrotic granulomatous nodules. (From Christian, Sarre, Peers, Salazar and de Rosario: A.M.A. Journal of *Diseases of Children* 92:66-74, July 1956.)

cases, Butt and Hoffman one.[?] I observed no signs of adrenal failu
in any of my cases although the adrenals had been partially destroyed
several. When miliary dissemination of the disease occurs the symptom
of toxicity are so overwhelming and fulminant that incipient adrenal in-
sufficiency would likely be overlooked. In more slowly progressive di
ease enough adrenal tissue usually remains to prevent clinically apparen
Addison's disease.

## Central Nervous System

Lesions of the central nervous system may occur in either (1) the parenchyma of the brain and spinal cord or (2) the meninges. The latter site is the more important by far.

Coccidioidomycosis sometimes produces solitary or multiple granulomas of the brain although it does so less commonly than such other mycoses as blastomycosis. The granulomas may be miliary or may be large enough to simulate a brain tumor. Rarely an actual brain abscess may be caused by *Coccidioides*. Rhoden described the fulminating illness of a diabetic 16 year old boy with headache anorexia and signs of meningeal irritation[41] Autopsy showed a large abscess almost replacing the left cerebellar hemisphere lined by a ragged membrane containing grey yellow pus and causing such swelling that the fourth ventricle was compressed and the third and lateral ventricles dilated.

Meningitis is the most significant coccidioidal lesion of the central nervous system. Among Caucasians it is the commonest cause of death from coccidioidomycosis. In some series it was present in one fourth of the cases of coccidioidal granuloma. No form of the disease is more invariably fatal.

The usual variety of coccidioidal leptomeningitis is in Forbus words "a firm plastic type of meningeal inflammation which results in the encasement of the brain substance particularly the brain stem in a rigid highly organized granulomatous mass of tissue[4] Perhaps the most characteristic feature of the disease from the clinical standpoint is the obstruction of the subarachnoid spaces and spinal fluid channels by the thick exudate causing the internal hydrocephalus which always develops if the patient lives long enough and which is itself eventually fatal.

Lesions are most extreme at the base of the brain. The leptomeninges are congested edematous and studded with opaque yellow grey nodules. Cerebral vessels are dilated. The brain is edematous its convolutions wide and its sulci narrow. There may be pockets of frank pus between the arachnoid and pia mater. The meninges of the spinal cord may show similar lesions.

Microscopically the meninges and adjacent brain contain tubercles and granulomas with occasional bi refringent endosporulating spherules. The longer the duration of the process the fewer the spherules likely to be found[9,7] Here and there are focal areas of suppuration.

Occasionally the granulomatous process is maximal in the spinal cord or its envelopes simulating a cord tumor. The lesion may begin in the spinal canal or it may extend from the vertebrae. Of Rand s two cases the first concerned an extra dural granuloma which penetrated the thoracic cavity[1,9] The patient had a spastic paraplegia and loss of all sensation

below the level of the compression Surgical removal of the lesion restored essentially normal motor function In several other cases constricting subdural granulomas of the thoracic or cervical cord caused paraplegia or quadriplegia loss of all sensation and death

In coccidioidal lesions of the spinal cord cerebrospinal fluid studies and myelograms are typical of complete block in the canal Fluid is deeply xanthochromic and coagulates readily Protein may be incredibly high—12 000 mgm per 100 cc in Gottlieb's case [819] The gold curve follows the so-called paretic pattern Roentgenograms may reveal vertebral erosion Decompression operations are often unsuccessful and the process is invariably fatal The spinal canal is filled with a tough purulent exudate The dura is greatly thickened so that the cord may appear twice its normal size although the cord proper may be but a strand of nervous tissue Necrosis may have rendered its structure unidentifiable

## Eye

The eyes are not commonly involved in either primary or secondary coccidioidomycosis Most of the few studies concerning ocular disease mention clinical rather than pathological findings Trowbridge has done most to describe and classify coccidioidal lesions of the eye [1]

Manifestations during the primary phase are usually associated with erythema nodosum and like it are evidences of hypersensitivity Phlyctenular conjunctivitis and episcleritis or keratitis are most common Scleral and episcleral blood vessels are engorged The conjunctivae may be thickened and hypertrophied There may be indurated elevations on the conjunctivae and sclerae Symptoms usually subside promptly but occasionally scleral hyperemia persists for several years

Levitt reported a case apparently concerning a primary infection in which both vitreous chambers were clouded by whitish appearing movable globular opacities [454] There were also small strands of connective tissue attached to hemorrhagic bases on the retina A month later the eyes were normal Lijo Pavia reported a somewhat similar retinal efflorescence in a fatal case [73]

Disseminated coccidioidomycosis not infrequently involves extra-ocular structures Granulomas of the eyelid or brow and abducens palsy in coccidioidal meningitis are for instance seen now and then Lesions in the eye itself are uncommon The first North American case of Rixford and Gilchrist is perhaps the most remarkable Opacities appeared in the corneas There was severe chemosis under the conjunctivae One eye was destroyed by a pyogenic infection complicating the granuloma The cornea of the other eye became so weakened that during a fit of coughing it gave way and the eyeball had to be removed

Forbus and Bestebreurtje tabulated two cases in which the optic nerve contained coccidioidal lesions but there was no elaboration of these data [40] Lovekin[648] and Conan and Hyman [78] have reported cases of disseminated disease in which retinal exudates hemorrhages and perivascular sheathing were seen on examination Pathologic studies could not be made

## Nasopharynx and Larynx

Coccidioidal granulomas of the tongue nose and throat are now and then part of widespread dissemination more rarely they represent the only detectable extra pulmonary lesions It was early noted that retropharyngeal abscesses may occur as the result of anterior presentation of suppurative lesions in the cervical vertebrae

Childrey and Gray described an extensive ulcerating granuloma of the posterior nasopharynx and trachea [147] Writing before the discoveries of Dickson and Gifford they thought the nasopharyngeal lesion represented the portal of entry for it antedated other disseminated lesions in a fatal infection In another case reported by several different authors [817, 881, 905] there were edema of the arytenoids ulceration of the laryngeal mucosa and a fungating granulomatous mass which obstructed the ventricles and eventually made a tracheotomy necessary Mumma described the case of a colored man with sore throat dysphagia hoarseness and blood tinged sputum whose only obvious lesion was a granuloma of the epiglottis and whose general health was good [70]

## Heart

Non specific myocarditis or specific granulomatous reactions in the myocardium have been described in about a quarter of some series of autopsy studies In a description of the histopathologic findings in four cases of disseminated coccidioidomycosis Reingold reported non specific myocarditis in three and a specific granuloma in one [617] In the series of Forbus and Bestebreurtje granulomatous lesions were found in 14 of 50 cases [40] The foci were for the most part tiny and infrequent Gore and Saphir reviewing the material at the Army Institute of Pathology (presumably including some of the data of Forbus) tabulated without further definition myocardial changes in 11 of 48 cases of coccidioidomycosis [43]

The pericardium is also occasionally involved in disseminated coccidioidomycosis In 7 of their 50 cases Forbus and Bestebreurtje reported that the myocardial granulomas mentioned above were so superficial that their eruption had resulted in pericarditis [40]

Pericardial granulomas may also occur without generalized dissemination Larson and Scherb reported the case of a 60 year old white man

who died after a brief episode of congestive heart failure.[8] Autopsy studies showed chronic adhesive pericarditis. Granulomas containing *Coccidioides* were found in the lung and in the pericardium. It is likely that the pericardial lesion did not represent dissemination in the usual sense of widespread hematogenous or lymphogenous seeding but was merely contiguous involvement of the pericardium from nearby infected lung in an otherwise benign primary pulmonary infection.

Rarest of all cardiac lesions are those of the endocardium, noted first by Epstein.[11] Townsend and McKey reported coccidioidal endocarditis in the case of a 3-week-old infant with fulminating dissemination.[6]

## Peritoneum

Like other serous surfaces, the peritoneum is often involved in widely disseminated coccidioidal disease. Occasionally peritonitis accompanies coccidioidomycosis of the female adnexa, in which case the process may regress after surgical removal of the diseased ovaries and tubes.[1,5] Sometimes ascites is the first symptom of generalized coccidioidomycosis. On occasion the etiologic diagnosis has been made by peritoneoscopy and biopsy. Peritoneal surfaces are studded with miliary tubercles or covered with thick granulomatous tissue.

## Gastrointestinal Tract

One striking difference between coccidioidomycosis and tuberculosis is that the former usually spares the gastrointestinal tract. Ophuls often made a point of the absence of lesions in the intestine even when nearly every other abdominal organ was riddled.[11] Fulminating coccidioidomycosis is occasionally ushered in by diarrhea, bloating, or constipation, but even then the bowel is free of lesions.

It has been noted in cases of co-existing tuberculosis and disseminated coccidioidomycosis that intestinal lesions, if present, contain *M. tuberculosis* but not *C. immitis*. In a case reported by Firestone and Benson, spherules were found in the lungs, liver, spleen, adrenals, kidneys, prostate, thyroid, meninges, brain, skin, tonsils, and lymph nodes. Tubercle bacilli were also found in the lungs, and although there were extensive tuberculous ulcers in the ileum, no spherules could be demonstrated in the latter.

Coccidioidal peritonitis often involves the serosal surface of the bowel as well as of the mesentery and parietal peritoneum, but coccidioidal granulomas in other layers of the intestinal wall are very rare. Cravens in 1931 reported the first case of actual coccidioidal invasion of the bowel wall.[1,4] Duemling in 1949 reported a fatal case of coccidioidomycosis in which lesions were found in the skin, lungs, and pericardium. In addi-

tion there were numerous ulcers throughout the small and large bowel. They measured about 2 x 4 mm, their long axes being transverse to that of the bowel.

Sometimes the gastrointestinal tract is involved secondarily. Caseating masses of lymph nodes, for instance, have been known to ulcerate into the stomach or esophagus.

It is not known why the gastrointestinal tract resists *Coccidioides immitis*. Tuberculosis, usually the bovine variety, can of course be contracted through the alimentary canal, manifesting itself classically as scrofula or tuberculous cervical adenitis. Coccidioidomycosis can apparently not be contracted thus. Lubarsky and Plunkett have shown that *Coccidioides* organisms, both in the vegetative and saprophytic cycle, can pass through the gastrointestinal tract of mice with harm neither to the fungus nor to the host.[81] Intestinal mucosa is not lethal to the organism, but neither is it invaded.

## Urinary Tract

The kidney has been involved to some degree in about half of the fatal cases of disseminated coccidioidomycosis. Forbus and Bestebreurtje reported gross and microscopic renal lesions in 30 of their 50 cases studied post mortem, an incidence exceeded among abdominal organs only by lesions of the spleen.[40] Rohn found that renal lesions were reported in the accounts of 27 per cent of 214 cases he collected from the literature.[86]

Lesions in the kidney are usually small miliary granulomas or abscesses scattered throughout the parenchyma. The renal pelvis and ureter, like the gastrointestinal tract, are almost always spared. Uncommonly the bladder is involved.

Erythrocytes and leukocytes are sometimes found in the urine. Rarely there is gross hematuria. I have seen a case of acute fulminating disseminated coccidioidomycosis in which there was heavy proteinuria. In massive miliary dissemination the fungus is now and then cultured from the urine, as in the case of Goldman and Movitt.[106]

## Male Genital System

The prostate is occasionally invaded in generalized coccidioidomycosis, but only rarely is this clinically evident. Forbus and Bestebreurtje found microscopic prostatic lesions in 6 per cent of their cases.[40] McDougall and Kleinman described a case in which there were, among other findings, hematuria, pyuria, an enlarged indurated prostate and bloody prostatic fluid.[3] *Coccidioides* organisms were found in material aspirated from the prostatic abscess.

Several cases of coccidioidal epididymitis have recently been reported[630, 66, 5, 871]. Most often the lesion has been the only extrapulmonary focus of coccidioidomycosis. In at least one case the epididymis has been only one of many sites of infection[66]. There has often been a long latent period up to several years between the primary infection and the obvious peripheral lesion. In several cases the lesion has apparently followed trauma to the testicle. The disseminated lesion might have been adequately combatted and eliminated had it not been for the trauma. In most cases the complement fixation titer has been fairly low and apparent cure has sometimes followed surgical extirpation.

In one case seminal ejaculate contained *Coccidioides* organisms, raising the question of possible inoculation of spherules into abraded mucous membrane of the female genitalia[illegible]. If such transmission should occur it presumably would cause a primary self limited lesion in the vast majority of instances.

Coccidioidal epididymitis closely resembles tuberculous epididymitis. The epididymis is thick, firm, nodular, enlarged and tender. Sometimes there is fluctuation and sometimes an overlying draining sinus. On section granulomas and tubercles containing spherules are found. Occasionally adjacent testicular tissue is also involved.

## Female Genital System

Coccidioidal infections of the internal genitalia of the female have been reported on several occasions[illegible, illegible, 8, 6]. Sometimes, as in the case of Conan and Hyman, endometrial coccidioidomycosis was merely part of generalized dissemination[8]. Because tubercles of the endometrium were the first clue to the diagnosis these authors made the surprising suggestion that the portal of entry was the post partum uterus. However the course was in general similar to that of other secondary infections so that there is no reason to suppose that the primary infection was other than respiratory. The disease was eventually fatal.

Sometimes the pelvic inflammation is the main extra pulmonary lesion. Characteristic symptoms are pelvic pain often associated with menstrual periods, profuse vaginal discharge, chills, fever, malaise and weight loss. Physical signs are lower abdominal distension, tender masses in the adnexal regions and great pain on manipulation of the cervix. Usually a diagnosis of the tubo ovarian abscess is made but the causative agent is not suspected. At operation typical findings are studding of the peritoneum with little white nodules reminiscent of those seen in tuberculous peritonitis and inflammatory masses involving the tubes, ovaries and uterus.

Removal of the diseased organs has in several cases been followed by regression of all symptoms, decrease of the titer of complement fixing anti

bodies and restoration of apparent good health.[109, 388] At other times fatal recurrences have taken place.[63, 844]

### Coccidioidomycosis and Pregnancy

Although the subject needs further study, there seems to be an exception to the general rule that women withstand coccidioidal infection better than men, in that pregnancy appears to increase somewhat the hazard of dissemination. In this respect coccidioidomycosis may be reminiscent of such diseases as poliomyelitis, in which the incidence of severe forms is increased by pregnancy. It must be noted, however, that the numbers are small and the risk slight. No one would advise coccidioidin-negative females to leave the endemic area during pregnancy![1]

Isolated examples of fulminating coccidioidomycosis in pregnant white women were reported long ago,[illegible] but the relationship of pregnancy to disseminated coccidioidal disease has been emphasized only recently. Morbidity data are inadequate and incomplete because primary coccidioidomycosis has not long been reportable and its incidence during pregnancy is therefore uncertain. Other sorts of data are nevertheless suggestive. In 1948, for instance, four maternal deaths were reported in Kern County, California; three of these were due to coccidioidomycosis.

In 1949 Smale and Birsner reported five cases of disseminated disease occurring during pregnancy in Kern County.[6] This series was expanded by Vaughan and Ramirez in 1951.[6] They studied 28 cases in which primary coccidioidomycosis was contracted during pregnancy, and five cases in which it had been contracted so recently that the complement fixation test was still positive. Their series included all such cases known to have occurred in Kern County between 1942 and 1940. There were 19 Caucasian women, 1 Mexican, 1 Chinese, and 7 Negro. The numbers are too small to analyze statistically, but certain inferences may be drawn. Dissemination occurred in all of the Negro women, in 2 of the Caucasians, and in the one Chinese, a total of 10 out of 28. Dissemination was rapidly fatal to all patients (except one who was still alive when the paper was written). There was a high incidence of meningitis. The later the onset of coccidioidal infection, the greater was the hazard of dissemination. The disease was contracted during the first trimester in 12 cases (with one instance of dissemination), during the second trimester in five (with two instances of dissemination), and during the third trimester in 11 (with 7 instances of dissemination). When the onset was during the first trimester the chief complication was a tendency to abort.

It is generally felt that the placenta is an effective barrier to the fungus and that congenital coccidioidomycosis does therefore not occur. This opinion stems from such studies as that of Cohen, who approached the

problem from two standpoints (1) the rarity of coccidioidin skin sensitivity in infants born in endemic areas[5,6] and (2) actual observations of infants born to mothers suffering from disseminated coccidioidomycosis[6,16] Among those he reported were two similar cases of pregnancy complicated by fulminating disseminated coccidioidomycosis in Negro mothers both of whom died of their disease soon after delivery of premature infants In one case a fetus of five months was stillborn and in the other the infant survived a month to die of aspiration pneumonia In both cases the placenta was studded with granulomas containing *Coccidioides* but no lesions were found in the cord nor in the body of the infant The umbilical veins and lymph nodes at the hilus of the liver were free of lesions The live born infant had at birth a complement fixation titer equal to that of its mother (positive at 1 32) but a month later it was positive at only 1 4 The infant s coccidioidin skin test was negative

Smith[6,7] has reported six cases in which blood from the umbilical cord has fixed complement four times at the same titer as the mother s and twice at one serial dilution less In one instance the serum of both the mother and the new born fixed complement at a 1 32 dilution Five months later the baby s titer had fallen to 1 4 although the mother s was unchanged

These data indicate that as in syphilis the complement fixing antibody may be passively transferred through the placenta This phenomenon does not in itself suggest congenital coccidioidomycosis

Tuberculous lesions are occasionally found in the viscera of new born infants of tuberculous mothers but as Cohen[6,18] has observed the tubercle bacillus is very much smaller than the spherule of *Coccidioides immitis* Whereas the tiny tubercle bacillus might conceivably pass through the placenta the spherule is usually several times the size of a red blood cell and the smallest endospore is only a quarter the size of a red cell so that placental transfer of the fungus would be more difficult

It must nevertheless be pointed out that two cases do not prove a theory At most they demonstrate that placental transfer of *Coccidioides* is not the usual course of events In several other cases placental transfer although by no means proven is at least one of the possibilities Such a case for instance is that of a three week old infant born in Chicago and never taken elsewhere who died of fulminating coccidioidomycosis[9] The mother had suffered monostotic coccidioidal osteomyelitis several years previously before she had come to Chicago but the lesion had long been closed The alternative to placental transfer appears to be fomite transmission unrelated to the mother s illness Congenital coccidioidomycosis must be rare indeed but more data are needed to prove that it is an impossibility

## COEXISTING COCCIDIOIDOMYCOSIS AND TUBERCULOSIS

Fungus infections are notoriously prone to complicate certain debil tating illnesses such as leukemia Hodgkins disease and other lymphoma aplastic anemia leukopenic disorders tuberculosis and diabetes[8, 9] Fung most likely to cause secondary infections are *Aspergillus Candida Crypto coccus Histoplasma* and *Mucor* Not all fungi however show this ten dency to invade secondarily Those with no such habit are *Actinomyce Nocardia Sporotrichum Blastomyces Coccidioides* and the varied orga isms of maduromycosis and chromoblastomycosis

Nevertheless although *Coccidioides* does not tend to follow in th wake of other diseases it is by the law of averages occasionally superim posed on other infections Because of the similarity of pathologic findin and symptoms coexisting coccidioidomycosis and tuberculosis have bee of great interest[39, 45, 5, 534, 91, 93, 617, 693, 736, 7, 701]

The combination of these two diseases is most often seen in tube culosis sanitaria located in areas where coccidioidomycosis is endemic Be fore pulmonary coccidioidomycosis was clearly recognized as an entit patients with Valley Fever were sometimes erroneously hospitalized i tuberculosis hospitals where they contracted tuberculosis Usually how ever the combination occurs when patients with old tuberculosis eithe active or quiescent contract primary coccidioidomycosis

Various intriguing situations have been reported One patient ha a tuberculous effusion on one side and a coccidioidal effusion on the other[4] Another had a coccidioidal cavity in one lung and a tuberculous cavity i the other the sputum containing organisms from both[9] Still anoth patient two years after suffering primary coccidioidomycosis develope a bronchopleural fistula and hydropneumothorax the fluid of which con tained both *C immitis* and *M tuberculosis*[4] A tuberculous cavity ha apparently ruptured into the pleura incidentally going through a later coccidioidoma *en route*

In a few cases disseminated coccidioidal disease has existed coinc dentally with tuberculosis either pulmonary or generalized Sometime tuberculous osteomyelitis occurs in one bone and coccidioidal osteomye itis in another[571] In at least one case both organisms have been foun in the same bone[647] Coexisting invasion of many viscera has been re ported but in such cases *Coccidioides* has spared the bowel althoug *Mycobacterium* has not

In 1953 two fairly large series of coexisting disease were reported I by Stein of Tucson Arizona[77] and 24 by Cotton Penido Birsner and Bal cock of Kern County California[736, 700] Enough cases have now been ob served to form conclusions concerning the pathogenesis and treatment o combined disease

It might be presumed that *coccidioidal infection of the lung would* weaken it and predispose to subsequent invasion by tuberculosis. However, the incidence of tuberculosis in areas where *Coccidioides* is endemic is certainly no higher than elsewhere. The incidence of tuberculosis in patients known to have had coccidioidomycosis is likewise no higher than would be expected by chance. It seems unlikely, then, that *Coccidioides* breaches the defenses to allow later invasion by *Mycobacterium*. A more plausible pathogenesis is that coccidioidal lesions erode the fibrotic walls of old tuberculous foci and liberate their bacilli, for local hyperemia and necrosis accompany pulmonary coccidioidal lesions. Nevertheless, it is the opinion of most observers in endemic areas that quiescent tuberculous infections must seldom be activated by primary coccidioidomycosis.

Coccidioidal cavities may be long-lived, and coincident tuberculosis may be contracted any time during their course. This has doubtless been the case in some instances of double infection. Similarly, solid coccidioidomas may persist for years, and erosion by a spreading tuberculous lesion may occur, as in a case described above.

The most common pathogenesis appears to be purely accidental development of acute coccidioidomycosis during the course of a tuberculous infection. In this situation it does not seem that the two diseases have an adverse influence on each other. Each runs its own course independently.[7]

*Chapter Nine*

# The Varieties of Coccidioidal Infection

THE WIDE variety of symptoms associated with coccidioidal infection has been appreciated ever since the historic work of Dickson and Gifford in 1937 Before that time only one tiny segment of the spectrum was recognized—that of progressive coccidioidal granuloma Now it is known that invasion by *Coccidioides immitis* is accompanied by syndromes which vary from asymptomatic to almost explosively fatal

*Coccidioides immitis* usually causes a mild primary pulmonary infection inapparent in 60 per cent of the cases In 40 per cent it varies from a vague non specific indisposition to an acute pneumonitis Rarely the portal of entry of *Coccidioides is extrapulmonary and the ensuing* primary lesion a benign peripheral granuloma

In a small percentage of the cases the invaded lung is left with a benign residual lesion either a cavity or a granuloma (coccidioidoma) Rarely the pericardium may also be the site of a benign chronic granuloma

In something less than 0 5 per cent of the cases primary coccidioidomycosis is followed by progressive generalized or disseminated coccidioidomycosis formerly called coccidioidal granuloma The generalized form of the disease may be either acute or chronic Miliary disseminated coccidioidomycosis and acute coccidioidal meningitis are rapidly fatal Chronic disseminated coccidioidomycosis chronic coccidioidal meningitis and isolated peripheral granuloma may persist for several years before recovery or death

A useful classification of coccidioidal disease is as follows

- I Primary Coccidioidomycosis
  - A Primary pulmonary coccidioidomycosis
    - 1 Asymptomatic
    - 2 Symptomatic
      - (a) Influenza like syndrome
      - (b) Pneumonia
        - (1) With pleural effusion
        - (2) With acute cavitation
        - (3) With acute pericarditis
  - B Primary extrapulmonary coccidioidomycosis

II Benign Residual Coccidioidal Lesions
- A Pulmonary
  1. Chronic coccidioidal cavity
  2. Chronic coccidioidal granuloma (coccidioidoma)
  3. Coccidioidal bronchiectasis
  4. Coccidioidal pulmonary fibrosis
- B Pleural
  1. Pneumothorax and hydropneumothorax
  2. Chronic coccidioidal empyema
- C Pericardial
  Chronic coccidioidal pericarditis

III Disseminated Coccidioidomycosis (Progressive, generalized or secondary coccidioidomycosis, coccidioidal granuloma)
- A Acute
  1. Acute miliary disseminated coccidioidomycosis
  2. Acute coccidioidal meningitis
- B Chronic
  1. Chronic disseminated coccidioidomycosis
  2. Chronic coccidioidal meningitis
  3. Isolated peripheral granuloma

*Chapter Ten*

# Primary Coccidioidomycosis



## PRIMARY PULMONARY COCCIDIOIDOMYCOSIS

ALTHOUGH there are several portals by which *Coccidioides immitis* might enter the body in actual fact it is almost invariably the respiratory tract which *is first invaded* Even *before the demonstration* of primary pulmonary coccidioidomycosis by Gifford and Dickson Ophuls had showed the unique importance of the lung [11] Only rarely does the fungus gain access via the skin [779]

### Types of Primary Pulmonary *Coccidioidomycosis*

(1) *Inapparent Infections* Most coccidioidal infections are asymptomatic During World War II a number of studies were conducted in which it was shown that coccidioidin skin sensitivity often appears in newly exposed personnel without any accompanying symptoms [334, 4] The conditions of these studies were ideal Troops new to endemic areas were skin tested on arrival and at intervals thereafter usually every month When

a previously negative skin test became positive, it was evident that infection had occurred in the interval. Infections of any consequence were reflected in the patient's sick call record. Other affected personnel were quizzed to see if less important symptoms had occurred. Sometimes men recalled minor respiratory symptoms, but often none whatever could be remembered despite the certain knowledge that infection with *Coccidioides* had been acquired in the interval.

Smith's studies of 1,351 infections occurring in three San Joaquin Valley Air Fields from 1941 to 1945 showed that 59.6 per cent were inapparent.[4,7] Only 24.6 per cent of the infections were diagnosed. Another 15.8 per cent caused minor symptoms which were either ignored or were interpreted correctly only in retrospect, after the conversion of the skin test from negative to positive.

(2) *Symptomatic Infections.* Primary coccidioidomycosis is a self-limited disease of a few days to several weeks duration. About 40 per cent of acute coccidioidal infections cause symptoms varying from insignificant to prostrating. In the mildest cases the patient may experience only vague malaise and fatigability. In other cases he may have transient fever and the generalized aching so often associated with influenza or "the grippe," *without any localizing respiratory signs or symptoms.* This type of infection has been called the "influenza-like syndrome" of coccidioidomycosis. Its true nature is usually overlooked either because the patient does not seek medical care or because the tests required for a specific diagnosis do not seem indicated for so mild a disease. The existence of such types of coccidioidomycosis has been revealed only by surveys of large population groups.

Infections severe enough to cause the patient to seek medical care are most often examples either of acute coccidioidal pneumonia or the more spectacular specific erythemas. Respiratory infections usually manifest themselves as either bronchitis or pneumonia. As Reimann has noted, primary coccidioidal pneumonia *may be clinically indistinguishable from* that associated with pneumococcus or streptococcus infections, tuberculosis, typhoid fever, psittacosis, Q fever, ornithosis, histoplasmosis and viral pneumonias.[61,64] Pulmonary infections may be complicated by (1) pleural effusion varying from insignificant to massive, (2) acute pericarditis and (3) acute cavitation. The latter is to be distinguished from the chronic pulmonary cavity which, together with other residual pulmonary lesions, will be described hereinafter.

## Incubation Period

The incubation period of primary coccidioidomycosis has been precisely determined by study of cases in which the exact time of exposure

was known as in infections acquired in laboratories of non endemic areas and infections following brief exposure to endemic areas [73] The usual incubation period is 10 to 16 days the extremes being 7 to 28 days [336]

## Symptoms

Acute pulmonary coccidioidomycosis is characterized by various combinations of the following symptoms

(1) *Fever* Fever is usually but not always present in symptomatic primary coccidioidomycosis It may be evanescent or stubborn lasting from a few hours to two months or more There is nothing pathognomonic about the course of the fever although in the uncomplicated case it usually rises gradually with diurnal variations until a peak is reached and then falls as steadily Undulations and recurrences suggest complications Dissemination of the disease is often heralded by a recrudescence of fever after a brief remission In other cases dissemination occurs without remission of fever after the primary stage The longer the period of initial fever the more likely is dissemination although this observation is by no means infallible Dissemination has been known to occur without any rise in temperature either during the initial phase or during the period of dissemination

In Willett s military cases the average duration of fever was four days in Caucasians and eight days in Negroes [39] In my experience the average of both is more nearly two to three weeks This discrepancy is doubtless due to the fact that a wider spectrum of disease was observed in Army Hospitals than in installations where only the more severe cases were hospitalized

The course of some infections is afebrile even in the presence of such other signs of activity as increased erythrocyte sedimentation rates and abnormal roentgenograms of the chest The absence of fever does not necessarily mean a good prognosis for progression of the disease may occur without it but in general there is good correlation between the height and duration of fever and the severity of the disease High spiking fevers with remissions and exacerbations are often seen in patients of dark skinned races when dissemination is impending

The height of the fever is as variable as its duration In mild cases it may be barely recognized In more severe cases it may rise to 105 F in the afternoon Chills and night sweats as in any febrile disease may occur

(2) *Pain* Chest pain is a common symptom and frequently the first In some series it has been the dominant symptom occurring in 70 to 90 per cent of the cases The discomfort is sometimes dull and constricting—more an oppression than a pain More often it is the typical pain of

pleurisy made worse by coughing or deep inspiration Frequently it is substernal Sometimes the pain is excruciating all but preventing respiration Now and again it appears so suddenly that trauma the fracture of the ribs myocardial infarction acute pericarditis or acute cholecystitis are suspected *Pleuritic pain is often accompanied by friction rubs and* sometimes by demonstrable pleural fluid The pain is usually transient disappearing after several days but occasionally vague aching persists for *several months*

Substernal pain on swallowing is occasionally seen sometimes severe enough to prevent the eating of solid food [61] It has been proposed that such dysphagia is due to mediastinal lymphadenitis

(3) ***Shortness of Breath*** Respiratory embarrassment is uncommon but it may accompany large pleural effusions, extensive pneumonia or more rarely still spontaneous pneumothorax

(4) ***Cough*** Cough of some degree is often present but it is less frequent and less severe than would be expected by a comparison with other respiratory infections In some series it has occurred in less than half the cases and has usually been non productive [44] My experience has been somewhat different perhaps because of the higher incidence of more severe cases with production of white purulent or even blood streaked sputum the rule rather than the exception Goldstein and McDonald like*wise found cough in 88 per cent of their cases production of sputum in* 66 per cent and hemoptysis in 18 per cent [40] The paucity of sputum in the experience of many has led them to minimize the possibilities of sputum examinations *in diagnosis of the disease However in experienced hands* and with proper methods sputum studies are often decisive In a series of 100 cases I found that in 76 per cent there was productive cough and in 44 per cent *Coccidioides* was found in the sputum *In summary it* appears that cough particularly a productive cough is by no means universal in coccidioidal infections but when present it may lead to the cor*rect diagnosis*

(5) ***Anorexia*** Anorexia of some degree usually accompanies the infection Sometimes it is so severe that the patient may lose 20 or 30 pounds during an illness of several weeks If no complications occur a vigorous appetite usually returns and weight is rapidly regained Occasionally however even in the uncomplicated case there is a long period of poor appetite and failure to gain When dissemination follows the anorexia of the primary stage may progress into profound cachexia

(6) ***Headache*** Generalized headache occurs in about a third of the cases sometimes being so severe that lumbar puncture is done in fear of encephalitis or meningitis Spinal fluid is normal in the acute stage Headache usually subsides in a week or so but occasionally it persists much longer

(7) *General Symptoms of Infection* Generalized aching myalgia and backache are often present Malaise and lassitude of some degree are common In mild cases these may be the only complaints without any findings indicating a respiratory infection Profound fatigability and lassitude may persist for months after an otherwise uneventful recovery Such residual symptoms are often alarming to the patient who is aware of the possibility of serious complications It is important that the physician remember the frequency of post infection lassitude so that he may reassure the patient who fears that his disease is becoming disseminated

On the other hand some patients show objective signs of the disease without proportionately severe symptoms They may feel better than the roentgenographic findings would indicate I once saw a nurse whose acute coccidioidal pneumonia was discovered only because a roentgenogram of the chest was required periodically She had continued on duty during the period of infection and only in retrospect recalled having felt vaguely under par

(8) *Pharyngitis* Mild sore throat and pharyngeal injection occur often enough to cause confusion of the diagnosis with the common cold or other respiratory illnesses

(9) *Cutaneous Manifestations* The cutaneous lesions of acute coccidioidomycosis are among the most dramatic findings although it is now known that they appear in only the small minority of cases The earliest skin lesion is a generalized fine erythematous macular rash which occurs in roughly 10 per cent of the cases It usually appears within a day or two after the first symptoms and subsides within a week The eruption often covers the whole trunk and extremities Sometimes it looks like the rash of measles and sometimes like urticaria These early cutaneous changes do not denote specific sensitivity to the fungus but are simply an example of the "toxic erythemas" which appear in many acute febrile illnesses They appear before sensitivity to coccidioidin is well established and do not represent the same sort of specific reactions as the later lesions

The specific cutaneous lesions of acute coccidioidomycosis are *erythema nodosum* and *erythema multiforme* Usually these appear several days—but at times as long as three weeks—after the onset of respiratory symptoms sometimes with a recrudescence of fever following a remission Occasionally when other symptoms are too mild to be noticed the specific erythemas are the only obvious manifestations of the disease More rarely yet erythema nodosum may precede by several days the first symptoms of a moderately severe respiratory infection It was the illness characterized by erythema nodosum which was originally recognized as the primary stage of coccidioidal infection In fact erythema nodosum is a *sine qua non* of the classical San Joaquin Valley Fever" of Gifford and Dickson

although by general usage "Valley Fever" now includes all sorts of coccidioidomycosis. A popular pre-scientific name of "Valley Fever" was "The Bumps."

The specific erythemas occur in about 5 per cent of all primary infections or about 20 per cent of those which are symptomatic. Erythema nodosum is associated with the development of a good immunity and usually indicates a good prognosis. It occurs more often in women than in men, or in about one quarter of all infections and 40 per cent of those clinically diagnosed in women. Frequently these allergic manifestations convert an otherwise inapparent infection into one which is unmistakable. The female predisposition to erythema nodosum, not apparent in childhood, becomes clear-cut after puberty. The specific erythemas are rare in Negroes, occurring in less than 1 per cent of symptomatic cases, and then usually in those of mixed ancestry. The predisposition to erythema nodosum occurs in inverse ratio to the predisposition to dissemination. White women are most likely to have erythema nodosum and least likely to have dissemination. Negro men are least likely to have erythema nodosum and most likely to have dissemination.

There has arisen in some quarters the legend that erythema nodosum effectively prevents any complications of the primary infection, such as dissemination or residual pulmonary lesions. In reaction to this idea, the inference is occasionally made that there is no association between erythema nodosum and a good immunity. The truth appears to lie between these two extremes. A review of the early work of Dickson and Gifford will dispel the first illusion. One of Dickson's first patients was the engineering student who developed coccidioidal skin lesions after having had erythema nodosum.[ ] The immediate occasion of Gifford's suggestion to Dickson that Valley Fever might be related to coccidioidal granuloma was her observation that in the histories of three cases of the latter mention was made of erythema nodosum. In one of Dickson's early papers, he said "We have seen . . . records of several in which coccidioidal granuloma developed after erythema nodosum." The concluding sentence in the same paper is "The acute illness, whether or not there is erythema nodosum, may progress to coccidioidal granuloma." In a recent review of cases from Kern County, California, Bisner mentions four in which erythema nodosum was followed by dissemination. In four others residual pulmonary cavitation followed—a complication not unexpected inasmuch as cavitation may occur in the presence of good immunity. When dissemination occurs after typical Valley Fever it often takes the form of meningitis.

It is nevertheless true that erythema nodosum is a good prognostic sign, for the incidence of dissemination following classical Valley Fever is considerably less than it is among primary infections without the specific

erythemas Although about one out of two hundred symptomatic primary infections may become disseminated Smith found that coccidioidal granuloma followed only one out of seven hundred attacks of erythema nodosum [5] Other statistics similarly confirm the infrequency of dissemination following erythema nodosum One may therefore conclude that although erythema nodosum has no magic power to prevent dissemination it is in general a favorable sign

The lesions of erythema nodosum are usually limited to the lower extremities They typically appear as a crop of bright red tender itching or painful raised nodules in the skin from a few millimeters to several centimeters in diameter They are firm or elastic and are deeply embedded in the skin The distribution is roughly symmetrical over the anterior tibial surfaces They may be more numerous around the knees and now and then extend up to the lower third of the thighs or even to the lateral surface of the thighs and buttocks The acute lesions regress in a few days changing in color from bright red to reddish purple and then to brown leaving dusky areas of pigmentation for several weeks or months

Although erythema nodosum is occasionally seen above the thighs erythema multiforme is the more common lesion on the upper half of the body (Fig 24) It is seen as a variety of reddish nodules macules papules and vesicles with circinate or marginate borders The common sites are the sides of the neck and face the "collar area" of the upper back and thorax the dorsal surfaces of the arms forearms and hands and the margins of the palms The lesions are red and fade to a purplish or violaceous hue Sometimes erythema multiforme occurs alone and sometimes with erythema nodosum of the legs The lesions usually appear in one crop but occasionally new crops appear over several weeks particularly after fatiguing exertion Pitting edema of the ankles may accompany erythema nodosum presumably because of interference with lymphatic drainage

The specific erythemas are associated with a strong sensitivity to coccidioidin and are often accompanied by manifestations in the joints and conjunctivae which are also allergic responses Occasionally skin testing with coccidioidin will precipitate an attack of erythema nodosum [3] When the skin lesions are present coccidioidin skin testing must be done with caution starting with high dilutions (1 1 000 or even 1 10 000) Exquisite skin sensitivity in association with erythema nodosum is also seen in primary tuberculosis of childhood It has been noted that children with erythema nodosum accompanying primary tuberculosis may react to only 1/10 000th as much tuberculin as is required in tuberculous children without erythema nodosum In primary tuberculosis erythema nodosum occurs

when the bacillus has completed its first stage of invasion, at which point sensitivity to tuberculoprotein is highest.



Figure 24. Erythema multiforme associated with acute primary pulmonary coccidioidomycosis. (From Gifford: *Annual Report, Kern County Department of Public Health*, 1935-1939, pp. 73-79.)

Winer has pointed out that the histopathological features of all types of erythema nodosum are identical, whether the associated disease is coccidioidomycosis, tuberculosis, rheumatic fever, tularemia, pregnancy, or drug reaction.[31] In the erythematous nodule there are mild polymorphonuclear infiltration of the skin, edema, acute arteritis, fibrinoid necrosis

histiocytic granulomas and polymorphonuclear and eosinophilic infil
tion of the subcutaneous tissues

(10) ***Joint Manifestations*** Arthritis often accompanies the spec
skin lesions of primary coccidioidomycosis giving rise to the popular na
"Desert Rheumatism It too is associated with high sensitivity to c
cidioidin It has been observed in about 8 per cent of some series
symptomatic cases At times there is nothing more than a vague arthral
without objective findings In other cases there may be exquisite p
on pressure or motion with only slight periarticular swelling stiffness r
ness or heat Effusion into the joint has not been observed Acute c
cidioidal arthritis may affect any joint—hips shoulders elbows wrists
fingers—but most often it involves the ankles and knees Sometimes o
one joint suffers and sometimes several at once or in succession
arthralgia may be as fleeting as the early skin lesions or it may per
for several weeks but it always clears without sequelae

The arthritis accompanying the primary stage is a sensitivity phen
enon organisms of *Coccidioides* are not present in the involved joints
this respect the lesion resembles that of acute rheumatic fever which r
resents the reaction of the articular tissues to the presence of streptoc
elsewhere in the body and not a streptococcal invasion of the affec
joints The septic arthritis of disseminated coccidioidomycosis is due
an actual invasion of the joint by the fungus whereas the arthritis of p
mary coccidioidomycosis is an allergic response Although the joint a
skin manifestations of primary coccidioidomycosis often occur simu
neously either may occur alone

(11) ***Conjunctivitis*** Inflammation of the conjunctiva is another m
ifestation of hypersensitivity in the acute stage Frequently it is o
shadowed by other more spectacular symptoms so that its exact incide
is uncertain It probably occurs at least as frequently as erythema nodos
and acute coccidioidal arthritis It may be simply an area of slight c
junctival injection or there may be conjunctivitis of the phlyctenular ty
episcleritis or keratitis Organisms of *Coccidioides* are not present in
eye

## Physical Findings

The physical findings in primary pulmonary coccidioidomycosis
usually not remarkable except in the presence of the allergic erythen
arthritis or conjunctivitis There is nothing pathognomonic about the
ease The patient looks like any other patient with a respiratory illn
with variable signs of fever cough and prostration Even in the prese
of pneumonia Caucasian patients usually have unexpectedly few si
of toxicity Negro and Filipino patients may appear more profoundly

There may be moderate pharyngeal injection. With coccidioidal pneumonia there may be rales or signs of consolidation. When pneumonia is accompanied by pleurisy there may be a pleural friction rub or signs of pleural effusion; when accompanied by pericarditis there may be a pericardial friction rub. *Peripheral lymphadenopathy is not seen in uncomplicated infections.*

*Laboratory Findings*

(1) *Hematologic Characteristics.* (a) *Leukocytes.* In about half of the cases the leukocyte count is moderately elevated, from 10 000 to 15 000. Occasionally it is over 20 000. There is rough correlation between the degree of leukocytosis and severity of the primary infection. *Early in the course of the disease there is an increase in immature leukocytes*; later there may be both a relative and an absolute increase in lymphocytes.

(b) *Eosinophiles.* The most important hematologic characteristic from *the standpoint of diagnosis is the frequent occurrence of eosinophilia.* Eosinophile counts of 4 to 10 per cent are almost the rule and in some series a quarter of the patients had counts of over 10 per cent. *It is* not rare to have eosinophile counts of 20 to 25 per cent. Willett has reported a case in which the total leukocyte count was 49 650 with 69 per cent eosinophiles.[48] Very high eosinophile counts are often associated with prolonged pulmonary infiltration and sometimes herald dissemination of the infection.

(c) *Erythrocyte sedimentation rate.* The hematologic test most useful for evaluating the progress of the infection is the measurement of the erythrocyte sedimentation rate. Almost invariably elevated early in the disease, it gradually falls with recovery. Failure to return to normal or continuing rise are suggestive of dissemination. The test is particularly useful in interpreting the significance of a positive skin reaction to coccidioidin. *A normal erythrocyte sedimentation rate essentially rules out active primary coccidioidomycosis even if the coccidioidin skin test is positive.* The reverse is of course not necessarily true; *a rapid sedimentation rate does not necessarily establish that a current illness is coccidioidal.* The sedimentation rate is also the most reliable single index of activity of a primary infection. It does not return to normal until after other signs of activity have disappeared. *It is therefore helpful in determining when it is safe to allow a patient to be up and around.*

(2) *Mycologic Findings.* Specific mycologic methods useful in diagnosis of coccidioidomycosis *are discussed in greater detail in Chapter Three.* The demonstration of *Coccidioides* in the sputum is theoretically at least the diagnostic method *par excellence.* It nevertheless has several practical difficulties *which must be taken into consideration.* Study of

a fresh smear is not always reliable for artifacts may be mistaken for spherules giving a false positive and spherules may be overlooked even when present giving a false negative Culture and even animal inoculation may be necessary potentially hazardous procedures requiring strict precautions Furthermore in mild cases it may be impossible to obtain sputum Even more seriously ill patients may not complain of cough It is nevertheless worthwhile to try to obtain a sputum specimen for examination If instructed to breathe deeply five or six times the patient may suddenly cough vigorously and produce material from far down the bronchial tree The difficulties attendant upon demonstration of the fungus often make serologic procedures the diagnostic methods of choice

(3) ***Immunologic Findings*** (a) *The coccidioidin skin test* The coccidioidin skin test should be performed immediately in each suspected case If negative it should be repeated in a week or two Coccidioidin skin sensitivity appears in from 2 to 21 days after onset and persists for 1 to 20 years or longer even for life Conversion from negative to positive is indisputable evidence of an active primary infection The test is discussed in detail in Chapter Six

(b) *Serological tests for coccidioidal infection* The precipitin test and complement fixation test are described in Chapter Six In primary infections they should be postponed until skin sensitivity appears for the skin is sensitive to coccidioidin before humoral antibodies are present If *Coccidioides* is found in the sputum serological confirmation is not necessary for diagnosis although it aids in judging the prognosis In acute infections precipitins appear first become maximal and recede fairly rapidly The presence of precipitins therefore establishes that primary coccidioidomycosis has occurred recently Complement fixing antibodies appear and disappear more slowly Humoral antibodies particularly those that fix complement may not be demonstrable in mild infections A rising complement fixation titer to a level of 1 32 or higher is an ominous sign

(c) *Serological tests for syphilis* Such tests as the Kahn and Wassermann are sometimes falsely positive in coccidioidal infections

(4) ***Electrocardiographic Findings*** In a significant number of cases (25 per cent in one small series) [46] electrocardiographic changes are noted during primary pulmonary coccidioidomycosis If acute pericarditis is present—an unusual complication—changes may be similar to those found in other varieties of pericarditis RS T segments may be elevated and T waves inverted in several leads In most cases changes if present at all are non specific Tudbury[8, 9] noted two types of changes (1) inverted flat or diphasic T waves and (2) low voltage of the QRS complex

## Roentgenographic Findings

The roentgenographic appearance of the lungs in primary coccidioidomycosis varies widely. It may be entirely normal or there may be extensive pulmonary infiltration, great lymphadenopathy or massive pleural effusion. Because they are asymptomatic, most cases of primary disease are not studied roentgenographically. The mildest infections, being only superficial inflammations of the bronchial mucosa or a few alveoli, cause no change in the thoracic shadow. At times, however, pulmonary abnormalities are noted even in asymptomatic cases. About 60 per cent of infections severe enough to require hospitalization cause pulmonary changes detectable roentgenographically.

There is nothing pathognomonic about the roentgenogram of primary coccidioidomycosis. It may mimic that of bronchitis, "atypical pneumonia," primary tuberculosis or even metastatic carcinoma. Various classifications, some very elaborate, have been made of the lesions of primary coccidioidomycosis.[314, 3, 411, 4, 4, 1] Such lists are useful for study and reference, but the individual roentgenogram often defies classification.

Primary coccidioidal lesions may occur in the bronchus, parenchyma, lymph nodes and pleurae. Peribronchial infiltrations may be represented only by fuzzy thickening of hilar shadows or by increased bronchovascular markings which radiate from the hili toward the base or periphery. Parenchymal lesions vary from a veil-like haze or vague mottling to dense homogeneous consolidations. Infiltrations may be peripheral densities, circumscribed and discrete, or they may be central, fanning out from the hili into the lung fields. There may be but one such patch or there may be a number throughout both lungs.

Lesions may exist in any part of the lungs, including the apices, but they are more likely to be in the lower lobes or base of the upper lobes. When they do appear in the apices they look much like reinfection tuberculosis. In severe infections, particularly in dark-skinned patients, a whole lobe or even more may appear almost solid, although usually the distribution is not strictly lobar. Coccidioidal pneumonia resembles atypical pneumonia more than bacterial pneumonia in that infiltrations are more uniform and circumscribed than in the latter.

Sometimes exudative lesions clear rapidly, in a week or two, but often resolution of dense consolidations is slow, requiring several months. Peripheral densities may not resolve completely, developing into fibrous nodules which persist for years. At first more or less diffuse infiltrations, they become smaller and more round, leaving a solitary nodule at the site of the previous pneumonitis. At times there is excavation of a zone of diffuse pneumonitis or of a nodule with formation of a cavity which may speedily close or which may become chronic.

Primary coccidioidomycosis may cause not only bronchitis and pneumonitis but also regional lymphadenitis. Although hilar lymph node enlargement may occur alone, it often occurs in conjunction with parenchymal lesions and it is commonly more evident on the side of the affected lung.



Figure 25. Mild coccidioidal pneumonitis and hilar adenopathy from which recovery was complete. Filipino farm laborer.

In more severe cases mediastinal nodes are also enlarged. In some series mediastinal lymphadenopathy was a constant finding in infections which later became disseminated, suggesting that the mediastinal lymph nodes are the second line of defense which must be breached if dissemination is to occur. Hilar lymphadenopathy may regress in a few days or weeks. If the mediastinal nodes are also involved, regression may take months even if dissemination does not follow.

Calcium is sometimes deposited in healed lesions of the lungs and lymph nodes, although calcified foci are less common in coccidioidomycosis than in histoplasmosis. Pleural effusion, often just enough to obliterate the costo-phrenic sulcus, is sometimes noted on the roentgenogram.

(Fig 26) It may be the only demonstrable abnormality Now and then spontaneous pneumothorax is seen in primary coccidioidomycosis



Figure 26 Coccidioidal pneumonia and interlobar pleural effusion occurring in a white male who later recovered completely

When the primary infection becomes rapidly disseminated serial roentgenograms may show steady progression of the pulmonary lesion until death ensues (Fig 27) Pneumonia is extensive and may be accompanied by pleural effusion The mediastinum is wide because of the inflamed lymph nodes *With miliary seeding the lungs seem to explode with fuzzy* little nodules which may soon become confluent

## Common Syndromes Suggesting Primary Coccidioidomycosis

Certain syndromes are especially suggestive of primary pulmonary coccidioidomycosis if there is any possibility of exposure by residence travel fomites or laboratory work

(1) *Erythema Nodosum or Multiforme* The specific erythema should suggest the possibility of coccidioidal infection even outside of the endemic area if there is any possibility of exposure In endemic areas erythema nodosum is generally considered to be coccidioidal until proved

otherwise Indeed care must be taken lest other causes of erythema nodosum be overlooked for tuberculosis streptococcal infections and other diseases will occasionally be responsible although the odds favor the diagnosis of coccidioidomycosis

(2) ***Acute Febrile Arthritis*** especially if associated with erythema nodosum or conjunctivitis



A B

Figure 27 Severe coccidioidal pneumonia occurring in a Filipino farm laborer A Tenth day of illness widespread involvement of lungs particularly of the left B Twenty third day of illness two days before death miliary nodules throughout both lung fields (heavier roentgenographic exposure than in previous film )

(3) ***Eosinophilia*** particularly in the presence of pneumonia or other respiratory disease

(4) ***Respiratory Infections During the Summer and Fall in an Endemic Area*** During a hot dry or windy season coccidioidomycosis should be considered in any febrile illness that is not otherwise obviously explained

(5) ***Febrile Illnesses Occurring in New Arrivals in an Endemic Area,*** particularly in those engaged in agricultural work

## Acute Complications of Primary Coccidioidomycosis

(1) ***Pleurisy with Effusion*** Mild coccidioidal pneumonia is frequently accompanied by a pleural reaction manifested by pleuritic pain variable friction rub and pleural effusion detectable only roentgenographically Occasionally pleural effusion is so massive that the thoracic cavity appears to be obliterated on one side In Ophuls first case the earliest in which the primary phase can be recognized a gallon of fluid" was removed by

thoracentesis.[14] Large effusions most frequent in members of dark skinned races are often followed by dissemination of the disease. Sometimes the pleural fluid is sterile; sometimes, even in benign infections without dissemination, the fungus can be cultured from it.

(2) *Pericarditis.* Larson and Scherb have shown that acute pericarditis may accompany primary coccidioidal pneumonia. Abbott has also recounted such an instance proved by pericardectomy. *It is surprising that it has not been reported more often, considering that pericarditis is not rare with other types of pneumonia such as viral or primary atypical pneumonia. Inflammation of the pericardium may occur* by direct extension from the contiguous lung and pleura or by indirect spread via the lymph channels of the mediastinum.

Pericarditis may be manifested by pain hardly distinguishable from that ordinarily seen in primary pulmonary coccidioidomycosis. A pericardial friction rub may be heard. The electrocardiogram shows changes in the RS-T segments and T waves characteristic of pericarditis. The roentgenogram of the chest shows the changes of primary coccidioidal pneumonia.

Coccidioidomycosis may rarely cause a residual granulomatous lesion leading to constrictive pericarditis indistinguishable from that of tuberculosis.

(3) *Acute Pulmonary Cavitation.* Serial roentgenograms made during the course of primary coccidioidal pneumonia sometimes demonstrate an area of transient excavation in the midst of consolidated pulmonary tissue. The lesion is more often than not an accidental discovery without symptoms or sequellae. It may persist for a few days or weeks before closing spontaneously. Occasionally it develops into the chronic pulmonary cavity described in Chapter Eleven. Except for somewhat closer observation and more restricted activity than might otherwise seem indicated, no special therapeutic measures are usually necessary.

## Chronic Complications of Primary Coccidioidomycosis

The chronic complications of primary coccidioidomycosis are dealt with in Chapters Ten and Eleven. There are two types of chronic complications: one benign and only occasionally important, the other malignant and frequently fatal.

Benign chronic coccidioidal lesions may occur in the lung, pleura or pericardium. Chronic pulmonary lesions are coccidioidal cavitation, coccidioidomas, bronchiectasis and fibrosis. Pleural lesions are essentially complications of pulmonary residuals, i.e., pneumothorax, hydropneumothorax and empyema. Pericardial lesions are rarely important but occasionally cause constrictive pericarditis.

The malignant complications of primary coccidioidomycosis are the various types of dissemination acute miliary dissemination chronic dissemination meningitis and the isolated peripheral granuloma

## Treatment of Primary Coccidioidomycosis

More fully discussed in Chapter Thirteen the treatment of uncomplicated primary pulmonary coccidioidomycosis is in general symptomatic Rest and analgesics are usually all that is required

## PRIMARY EXTRA PULMONARY COCCIDIOIDOMYCOSIS

Although it has been generally believed that the injured skin is an important portal of entry of *Coccidioides immitis* a critical evaluation of reported cases shows this to be more legend than fact Intradermal or subcutaneous inoculation of the fungus is of course possible for it is used in animals is the final step in identifying *Coccidioides* The practical importance of the dermal route in human primary infections is however quite another matter

The legend of primary cutaneous coccidioidomycosis arose in the early twilight of incomplete knowledge about the disease when only the progressive granuloma was recognized as coccidioidal In the first case to be reported in North America the initial lesion was said to be a somewhat elevated tender red spot on the back of the neck" where the collar band rubbed [8] In his 1905 paper summarizing all the then known facts about the disease Ophuls stated that "all former cases seem to be examples of primary infection of the skin He rightly inferred that the lung was an important portal of entry however and concluded that "the infection may primarily be either a cutaneous or a pulmonary one

Because the first known lesion was on the skin many early cases were considered to be examples of cutaneous inoculation particularly when trauma could be related to it The reason for this false inference is now obvious For 42 years the only known form of coccidioidal disease was the disseminated When a lesion appeared on the skin of a person previously thought to be well it was natural to assume that the fungus entered at that point Now it is possible to reconstruct the true sequence of events in such cases The actual invasion of the fungus via the respiratory tract had been asymptomatic or undiagnosed Dissemination had occurred through the blood and lymph channels to the skin and other organs The cutaneous lesion was merely the first obvious evidence of dissemination Subsequent lesions thought to have developed from that in the skin were simply signs of more widespread dissemination from the lungs

Despite the clarification of the relationship of primary and secondary coccidioidomycosis by Gifford and Dickson the legend of the cutaneous

route of inoculation has persisted and is still given credence in current textbooks, reviews, and case reports.[1] Although the skin is a possible portal of entry, it is not an important one. Proven cutaneous inoculation has been rare. The problem was clarified by Wilson, Smith, and Plunkett in their report of an unquestionable case of primary cutaneous coccidioidomycosis.[2] They accepted as proved but one previously reported case, that of Guy and Jacob,[7,8] whose patient was inoculated with *Coccidioides* by the prick of a cactus thorn. At least one subsequently published case may also be accepted as genuine.[9,10]

In the case reported by Wilson, Smith, and Plunkett, spherules were introduced into the severely abraded skin of the finger of a mortician when he embalmed the body of a victim of disseminated coccidioidomycosis. Four days later the finger became swollen, red, and tender. There was transient fever. An indurated granuloma, centrally ulcerated, appeared at the site of the inoculation and healed slowly over the course of 60 days. Several firm subcutaneous nodules appeared on the back of the arm, and epitrochlear and axillary lymph nodes became enlarged, tender, and fluctuant. *Coccidioides* was isolated from the initial lesion and from the axillary nodes. The serologic pattern was typical of moderate primary coccidioidomycosis. The precipitin titer for coccidioidal infection became maximal and then disappeared; the complement fixation titer rose to 1:4 and then fell.

The first laboratory inoculation made by Rixford[5] into the skin of a dog produced a primary lesion almost identical with that described by Wilson, Smith, and Plunkett, but the significance of that early experiment has never been appreciated. The animal suffered a local skin lesion and regional lymphadenitis. Then, except for secondary bacterial infection, it recovered spontaneously without progressive coccidioidal granuloma— "none the worse," Rixford said, for the experiment.

The criteria for diagnosis of primary cutaneous coccidioidomycosis proposed by Wilson, Smith, and Plunkett are:

(1) There should be no history of significant pulmonary disease immediately preceding the appearance of the cutaneous lesion.

(2) The history should be suggestive of inoculation through a break in the skin at the site of the first cutaneous lesion observed. "Simple injury" such as a bump or bruise should be considered insufficient evidence.

(3) Only a short inoculation period should elapse, probably between one and three weeks, before a visible cutaneous lesion develops.

(4) The primary lesion should resemble a "chancre" as seen in primary syphilis or the primary cutaneous tuberculous complex rather than an abscess or torpid cutaneous ulcer. The lesion should be a relatively painless, firmly indurated nodule or nodular plaque with central ulceration.

(5) The precipitin reaction to coccidioidin should soon become positive. It should decline somewhat more slowly than if the disease had been present in the lungs for a few antecedent weeks.

(6) The response to the intracutaneous injection of coccidioidin should become positive and should increase in sensitivity (1:1000 dilution) unless immunity fails to develop.

(7) The complement fixation reaction should be negative at first and remain so for several weeks, after which it should be present only in low titer unless immunity fails to develop.

(8) Lymphangitis and lymphadenopathy should develop, but in the region of drainage only. Development of nodules similar to those seen in sporotrichosis may be expected.

(9) Spontaneous healing of the "primary" cutaneous syndrome should occur within a few weeks (unless the patient is immunologically defective; this should be anticipated in but one or two per thousand instances).

*Chapter Eleven*

# Benign Residual Coccidioidal Lesions



ALTHOUGH primary coccidioidomycosis almost always regresses spontaneously, it often leaves its scar in bronchial or pulmonary tissues. Birsner, writing from wide roentgenologic experience in the southern San Joaquin Valley, notes that *in his area "it is unusual to see a completely normal* roentgenogram of the chest in an adult."

Frequently it is impossible to prove that pulmonary fibrosis or bronchiectasis are causally related to coccidioidomycosis, but in the opinion of many such lesions are seen more commonly in endemic areas than elsewhere.

## CHRONIC COCCIDIOIDAL CAVITATION OF THE LUNG

One of the classic roentgenographic findings in coccidioidal disease is the *"thin-walled cavity"* (Fig. 28). It was first reported by Furness and Mills, and then by Yegian and Kegel. The definitive description of the lesion was made by William Winn, Medical Director and Superintendent of the Tulare-Kings Counties Tuberculosis Hospital at Springville, California, in a series of studies between 1941 and 1952. *Although not pathognomonic, the thin wall with little reaction around* it strongly suggests coccidioidomycosis. On the other hand, an area of reaction and a thick wall do not rule out coccidioidal disease.

of the acute pulmonary lesion. It typically appears at the site of the previous pneumonia. There may be excavation of an area of fibrosis. Sometimes a nodular lesion appears first, with subsequent central necrosis and evacuation of its contents via a communicating bronchus.

***Symptoms.*** Chronic coccidioidal cavities are often symptomless. In Smith's series of 153 cases of pulmonary cavitation diagnosed in the military services, 88 or 58 per cent were silent lesions, being discovered only by routine roentgenographic surveys.[3] Of those with symptoms, 17 per cent were noted in the course of acute coccidioidomycosis, 15 per cent suffered hemoptysis, 6 per cent had chest pain, and 4 per cent had cough, malaise, fever or sputum. In civilian practice, where routine roentgenographic studies are less common, most of the cases are diagnosed because of hemoptysis. In Winn's series of 92 cases, hemoptysis—varying from blood streaking to frank hemorrhage—occurred in two thirds.[6,7] Secondary infection occurs occasionally. Usually, except for annoying hemoptysis, the patient is in good health.

***Laboratory Studies.*** Hematologic studies are usually normal. The erythrocyte sedimentation is not ordinarily accelerated. Unlike the situation in severe disseminations, the coccidioidin skin test usually remains positive, although in an appreciable number of cases there is anergy even to a dilution of 1 to 10. Unless the primary infection is not long past, the precipitin test is negative. If complement fixation persists, it usually does so in low titer. In Smith's series,[3] the sera of only three fifths fixed complement in diagnostic titer (at least 4 plus at 1:2). A quarter were entirely negative. Less than half of those with positive tests had titers higher than 1:2. Less than a fifth were higher than 1:4. Although I have seen a maximal titer (1:256) associated with a coccidioidal cavity, this combination must occur very rarely.

With encouragement it is almost always possible to obtain sputum from a patient with a coccidioidal cavity, even when he does not complain of hemoptysis or cough, and the fungus is usually recoverable therefrom. Spherules are frequently reported in the sputum on direct smear, and Fiese, Cheu and Sorensen have also described the finding of mycelial forms in freshly obtained sputum. At times the sputum contains flecks suggestive of the "sulfur granules" of actinomycosis, which when examined under the microscope are seen to be tangled masses of hyphae.

***Roentgenographic Findings.*** The "typical" coccidioidal cavity is thin walled and cyst like, with no surrounding reaction. Often, however, the wall is not "typical" but is thick and bordered by a fairly dense pulmonary shadow, in which case it cannot be differentiated roentgenographically from a tuberculous cavity or even a lung abscess. Usually there is a single cavity

sometimes there are several Frequently a large cavity if secondarily infected contains a fluid level (Fig 29)



Figure 29 Secondarily infected thick walled coccidioidal cavity with fluid level (From Winn Coccidioidomycosis in Hinshaw and Garland *Diseases of the Chest* Philadelphia and London W B Saunders Company 1956 )

***Pathologic Findings*** Cavities vary in diameter from a few millimeters to many centimeters The cavity may be surrounded by atelectatic lung tissue and interstitial fibrosis sometimes with parenchymal tubercles and alveolar epithelialization The cavity itself is lined by a tough fibrotic membranous wall often covered by a shaggy exudate containing spherules or even hyphae of *Coccidioides immitis* The lumen may communicate with a bronchus Sometimes the cavity is more or less filled with a loose necrotic amorphous material also containing the fungus Occasionally the contents are frankly purulent

***Complications*** Hemoptysis mentioned above is the most common complication being reported in two thirds of some series[6 7] Usually it is minimal but occasionally it is massive having been fatal in at least two cases[849] Sometimes bleeding occurs only during respiratory infections Secondary infection occurs now and then Cotton feels that progressive enlargement of the cavities is due to superimposed bacterial infection[849]

Rupture of a peripheral cavity may cause pleural effusion empyema spontaneous pneumothorax or bronchopleural fistula

***Treatment*** Therapy of coccidioidal cavities, discussed more fully in Chapter Fourteen, is a subject of considerable difference of opinion. Some favor ignoring the lesion if it is asymptomatic, reserving surgical resection for cases in which there are severe symptoms. Others favor removal of all cavities to forestall complications.

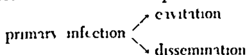
***Coexisting Chronic Cavitation and Disseminated Coccidioidomycosis*** It has often been noted that chronic pulmonary cavitation and dissemination rarely coincide. Sometimes this fact is presented as if some mysterious influence guarded the patient with a cavity. Probably it is just a matter of statistical chance. Neither dissemination nor cavitation are common sequellae of primary coccidioidomycosis; it would be even less common for them to coincide. Cavitation does not prevent dissemination; nevertheless, cavitation is usually associated with good immunity. Dissemination therefore would be expected to occur only rarely in the presence of cavitation. Dissemination follows one in several hundred primary infections; *there is no reason why dissemination could not accompany one* in several hundred pulmonary cavities.

Although cavitation is usually accompanied by a low titer of complement fixation, there is very occasionally a titer in the range of dissemination. One of my patients with a cavity of some two years duration had a complement fixation titer of 1:256. This case is almost unique, the incidence of such titers in cavitation being so low as to be recorded at zero in Smith's cumulative series.[9]

Cases of coincident dissemination and cavitation are so rare that they are still worthy of publication even in endemic areas. Interestingly, several of them concern concomitant meningitis and cavity. Chronic coccidioidal meningitis is also usually accompanied by low serologic titers and is usually the only extra-pulmonary lesion.

Smith and his associates,[3] Jenkins and Postlewaite,[61] Nillsen and Youssy,[419] and Timmes and Baum[141] have each reported a case of coincident meningitis and cavitation. Kurz and Loud also reported the case of a young man with cavitation in the presence of transient disseminated skin lesions.[411]

When cavitation and dissemination coincide, it is improbable that dissemination takes place from the cavity. More likely both are sequellae of the primary infection. The relationship can be diagrammed thus:




rather than thus:

primary infection → cavitation → dissemination

Furthermore, disseminations do not occur with excisional treatment of cavities.

## COCCIDIOIDOMA

Variously called the residual nodular density, benign pulmonary granuloma, coccidioidal tumor of the lung, solid fibrocaseous granuloma, and coccidioidoma, this lesion is rarely important per se but is mischievous because of the differential diagnosis it demands. The solid tumor of the lung is essentially a scar at the site of previous pneumonitis. It varies in size from the smallest detectable nodule—a few millimeters in diameter—up to 4 or 5 centimeters across (Fig 30). Such nodules may be single or multiple.

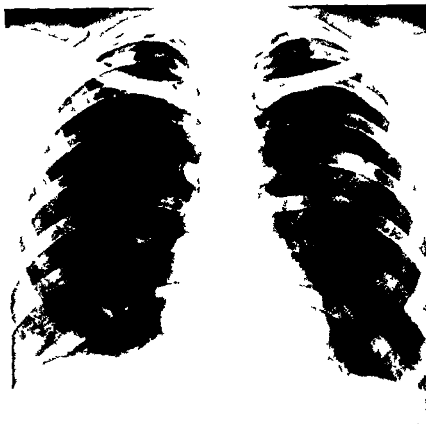


Figure 30 Large asymptomatic coccidioidoma of the apex of the left lower lobe (From Fiese, Cheu and Sorensen, *Annals of Internal Medicine* 43 255-270, August 1955.)

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The nodular residual pulmonary lesion has in the past been termed a "coccidioma" as that of tuberculosis is called a "tuberculoma." However "coccidioidoma" is more accurately derived from *Coccidioides*. "Coccidoma" suggests coccidiosis, the protozoal disease of chickens. Parallel forms would be "*Coccidia*," "coccidial," and "coccidioma" (if there were such a tumor in affected chickens) and, in the disease under discussion in this book, "*Coccidioides*," "coccidioidal," and "coccidioidoma."

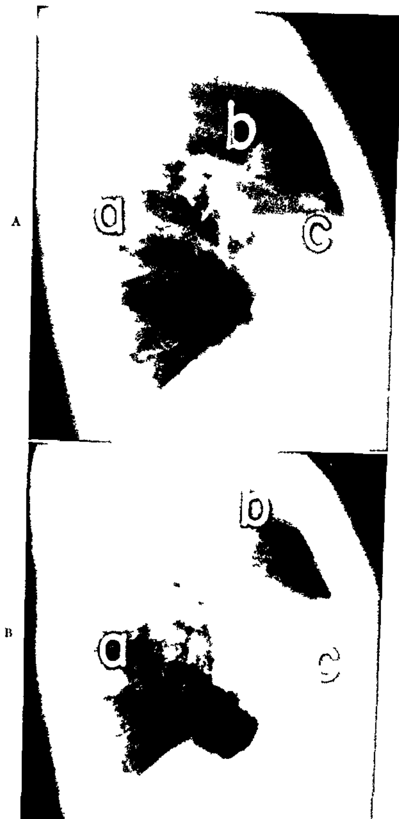


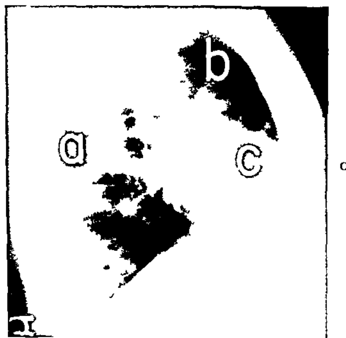

Figure 31. Serial changes in multiple residual coccidioidal lesions of the lungs. There are three large pulmonary lesions: (a) right lung, posterior; (b) left lung; and (c)

Long before his definitive description of primary coccidioidomycosis Dickson reported a case of benign pulmonary granuloma [49] The lesion puzzling to physicians of the time was one of the first clues that there might be a non malignant form of the disease Writing in 1915 Dickson described the benign coccidioidal lesion which had incidentally been found in the lung of a man who died of gastric carcinoma Ophuls microscopic examination was recorded thus

> A section of the lung shows large old caseous areas surrounded by dense fibrous tissue At the edge of the caseous material there are a number of double contoured capsules of the *Oidium coccidioides* The majority of them are empty but some contain a little granular protoplasm Diagnosis Healed coccidioidal granuloma of the lung

In 1939 shortly after the discovery of primary coccidioidomycosis Cox and Smith reported four cases in which pulmonary granulomas were accidentally found in routine autopsies

***Pathogenesis*** Now and then serial roentgenograms taken during and after coccidioidal pneumonia will nicely demonstrate the evolution of coccidioidomas During the acute stage there are fuzzy patches of pneu




right lung anterior A (a) is a thin walled cavity (b) and (c) are solid B five months later (b) is now a thin walled cavity (a) and (c) are solid C three months later all three cavities are now half filled with fluid Courtesy of Drs K W Butler and E Aronstein

months which later become smaller denser and more circumscribed persisting thus in some cases for many years Occasionally they become calcified

Coccidioidomas and cavities are sometimes but various stages of the same lesion (Fig 31) Alznauer Rolle, and Pierce[34] have pointed out that the residual pulmonary lesion is not necessarily a stable one for it may serially be a cavity solid tumor and cavity again as it fills and empties Winn[96] has termed such lesions abscessing coccidioidomas Cotton[419] differentiates between true coccidioidomas and pseudococcidioidomas in that the latter are cavities which become filled with inspissated material following obstruction of a communicating bronchus

***Pathology*** Often arising from a conglomeration of tubercles and fibrosis coccidioidomas may be lobulated and somewhat irregular in outline A firm capsule of hyalinized fibrous tissue delimits the mass Adjacent pulmonary parenchyma contains satellite tubercles and microscopic nodules The center of the lesion is soft yellow or gray necrotic, and caseous Microscopically the material is loose amorphous and occasionally even semipurulent Varying numbers of *Coccidioides* organisms are present sometimes so scantly that special stains are required for their demonstration Often the organisms are atypical—either degenerating spherules or abortive mycelial fragments suggesting that the necrotic debris is an unfriendly medium for perpetuation of the fungus in either the parasitic or saprophytic phase Spherules may be empty ghosts or wrinkled distorted capsules distinguishable only by their degenerating endospores Usually however even in ancient lesions enough viable organisms remain to give a positive culture When erstwhile solid granulomas become more or less excavated the fibrous capsule partially lined by vascular granulation tissue becomes the wall of a cavity

***Symptoms*** Solid granulomas usually cause no symptoms whatever If they become excavated they may bleed or become secondarily infected Almost always they are found unexpectedly on routine roentgenographic studies of the chest

***Laboratory Findings*** Because solid residual lesions are not associated with cough there are no typical findings in the sputum Unless there is communication with a bronchus and partial excavation fungi are not demonstrable The coccidioidin skin test is often positive but serologic titers are almost never high and are often not diagnostic In three quarters of the cases the titer of complement fixation is 1 2 or less Only rarely is it above 1 8 The erythrocyte sedimentation rate is not accelerated and other hematologic studies are also normal

***Roentgenographic Features*** The only significant finding in cases with coccidioidomas is the demonstration of circumscribed densities either isolated or multiple on the roentgenogram There is nothing distinctive about their appearance—and therein lies their only importance

***Significance of the Coccidioidoma*** Were absolute diagnosis of solid pulmonary tumors possible the coccidioidoma would be of academic interest only Unfortunately it looks exactly like other tumors of the lung benign and malignant Even in non endemic areas the coin lesion is an annoying problem The proportion of carcinomas among "coin lesions" varies directly with the distance away from an endemic area In some of the series collected in clinics in eastern states malignant tumors comprise up to half of such lesions[8, 1, 1, 6] In Portland Oregon a western city outside of the endemic area Higginson and Hinshaw reported that only 15 per cent of solid tumors were malignant and 18 per cent were coccidioidal[69] Winn and Evans have found that among residents of the San Joaquin Valley less than 1 per cent of "coin lesions are malignant[9, 5] When studied with appropriate stains most "tuberculomas" prove to be of fungal rather than tuberculous origin[6, 1, 83]

Nevertheless even in endemic areas surgically curable carcinomas of the lung occur so that undiagnosed pulmonary tumors must for the present be considered malignant until proved otherwise This attitude will be modified in the young patient with serologic evidence of coccidioidal infection but the diagnostic dilemma is still acute It is unfortunate that many benign lesions must be removed in order to save the man with the operable pulmonary carcinoma but as thoracic surgery has become increasingly safe its hazard has become less than that of overlooking a malignant lesion

## BRONCHIECTASIS

Primary coccidioidomycosis is often an endobronchial disease Bronchoscopic studies by Cotton and Birsner [1] have emphasized the frequent presence of bronchial lesions (mucosal hyperemia submucosal edema and ulceration or granulation tissue formation) sometimes without demonstrable pulmonary infiltrations

If acute bronchitis of varying degree is an important lesion produced by *Coccidioides immitis* one would expect bronchiectasis to be an occasional sequel Exact data are hard to develop but many clinicians in endemic areas feel that bronchiectasis is more common there than elsewhere[669, 7, 1] In any case bronchiectasis is often temporally related to primary pulmonary coccidioidomycosis and spherules have been found in the walls of bronchiectatic cavities Winn[3] reported the case of a young woman who in her teens developed a persistent cough occasionally pro

ductive of blood streaked sputum Roentgenographic studies over the next decade showed slowly progressive bronchiectatic changes and *Coccidioides* was finally found in the sputum

Birsner [51] has published roentgenographic demonstrations of bronchiectasis accompanying coccidioidal cavitation and fibrosis Roentgenographic studies in one of my cases showed numerous densities in the right middle and lower lobes Mycelial forms of *Coccidioides* were found in the sputum [5] In the surgically resected lobes there were bronchiectatic cavities containing large numbers of mycelial elements of the fungus

Coccidioidal bronchiectasis may cause chronic productive cough hemoptysis and recurrent fever and respiratory infections The complement fixation titer may be higher than that in typical benign coccidioidal cavitation of the lung Resectional surgery is indicated if symptoms are progressive or severe

## COCCIDIOIDAL PULMONARY FIBROSIS

The most common but least discussed sequel of coccidioidal pneumonia is pulmonary fibrosis Usually this is a more or less insignificant linear streaking in the lung the last stage of healing but now and then




Figure 32 A Severe acute coccidioidal pneumonia occurring in a Negro male B Over three years later extensive residual pulmonary fibrosis There were also disseminated coccidioidal lesions of the bones and skin of the hand

it is extensive After severe primary infections and in the presence of extrapulmonary dissemination there may be long persistence of large pulmonary densities (Fig 32) the so called chronic coccidioidal pneumonitis

Fibrotic areas consist of connective tissue masses containing lymphocytes, occasional multinucleated giant cells and microscopic tubercles. Sometimes the remains of spherules are seen. Occasionally there are calcium deposits dense enough to show up on roentgenograms. Large areas of fibrosis may caseate and become excavated. A lobe badly damaged by *Coccidioides* may at the same time show fibrosis, bronchiectasis and cavitation.

Residual fibrosis is usually of no importance, although it may cause diagnostic confusion with more serious diseases such as tuberculosis or even bronchogenic carcinoma. Even if extensive, it is the accompanying process—cavitation, bronchiectasis or extra-pulmonary dissemination—which is important.

## CHRONIC COCCIDIOIDAL EMPYEMA

Coccidioidal empyema may occasionally follow the pleural effusion of primary pulmonary coccidioidomycosis or it may result from rupture of a chronic coccidioidal pulmonary lesion into the pleural space, either spontaneously or during a surgical procedure. Although the process may be benign in the sense that it does not represent extra-thoracic hematogenous dissemination with failure of immune mechanisms, it may be a severe debilitating illness. Sometimes multiple draining sinuses burrow to the surface. Secondary surgical procedures such as thoracoplasty or decortication are often followed by healing.[19] In other cases further surgery seems only to spread the infection. Occasionally the general effect on health may be as terrifying as that of widespread dissemination.

## PNEUMOTHORAX AND HYDROPNEUMOTHORAX

Rupture of a peripherally located coccidioidal cavity may lead to pneumothorax, hydropneumothorax or bronchopleural fistula. The accident may cause reappearance of precipitins.[6, 6]

## CHRONIC COCCIDIOIDAL PERICARDITIS

The pericardium may rarely be permanently affected, as in the case of chronic granulomatous pericarditis reported by Larson and Scherb.[7, 8] Although mechanical constriction of the heart was fatal in that instance, the lesion was benign in the sense that it was localized, non-progressive and essentially burned out, an anatomic relic of the primary infection.

*Chapter Twelve*

# Disseminated Coccidioidomycosis (Generalized, Progressive, or Secondary Coccidioidomycosis; Coccidioidal Granuloma)



DISSEMINATED coccidioidomycosis is the relatively rare complication of primary coccidioidomycosis in which *Coccidioides* escapes from the lungs and mediastinal lymph nodes to invade other tissues and organs. Dissemination of the organism via the lymphatics and blood stream usually occurs during or soon after the primary phase. Late dissemination from an old focus in the lungs does not often occur because of the protective immunological mechanisms by then established. Viable organisms escape from the lung and colonize other organs because of a hiatus in the immunity response of the host's body. Seeding of the fungus throughout the body may be on so slight a scale or so well combatted that it is inapparent except for persistently elevated serologic titers, or it may be so vast that miliary abscesses appear in almost every cubic inch of body tissue and death speedily follows. The degree of dissemination is commonly somewhere between these two extremes, with obvious invasion of one or several

extrapulmonary sites The outcome depends on the number and location of the lesions and whether the host can tardily rally his immunologic defenses

The spectrum of secondary coccidioidomycosis may be conveniently divided into several parts although there is overlapping one on the other (1) Acute (a) miliary dissemination (b) meningitis (2) Chronic (a) generalized dissemination (b) meningitis (c) isolated peripheral granuloma and (d) inapparent dissemination The mortality varies with the type The over all mortality of progressive coccidioidomycosis is about 50 per cent The mortality of acute miliary dissemination and of meningitis is essentially 100 per cent The prognosis of isolated peripheral granuloma is best of all if the lesion remains localized on an extremity life is spared The course of chronic dissemination varies It may be slowly downhill to death there may be long persistence of lesions without much effect on general health or there may be gradual healing and eventual recovery after several years

## TRANSITION FROM THE PRIMARY TO THE SECONDARY STAGE

Although the exact instant when a hitherto localized pulmonary infection becomes irretrievably disseminated is not detectable the catastrophe can often be rightly suspected Sometimes of course when the primary infection has been asymptomatic or overlooked the first sign of disease is the extra pulmonary lesion Coccidioidal meningitis in Caucasians for instance often appears insidiously

When dissemination of the fungus is massive there is no intervening period between the primary and secondary phases Most common in Negroes and Filipinos this sequence is characterized by a severe primary illness progressing relentlessly to death while new verrucous skin lesions and subcutaneous abscesses appear almost daily

Less massive dissemination is often reflected by a characteristic clinical picture The patient first has coccidioidal pneumonia somewhat more severe than the average It may have noteworthy features such as a large pleural effusion or remarkable eosinophilia After several weeks the temperature falls and recovery seems imminent although the sedimentation rate remains elevated Then a few days later fever recurs appetite fails the complement fixation titer starts to rise and in a month or so the abscesses or verrucous skin lesions of disseminated coccidioidomycosis appear The second bout of fever may regress after another six or eight weeks leaving the patient with the chronic form of secondary coccidioidomycosis

Again the secondary phase may appear even more insidiously Partial recovery follows the initial pneumonia Fever disappears the pul

monary lesions regress and the patient is able to be up and around but lassitude, anorexia and fatigability may persist. Then without much in the way of general symptoms ulcers or abscesses appear on the skin and the downhill course is under way.

## INAPPARENT DISSEMINATION VS "LATE DISSEMINATION"

Dissemination may be inapparent if but a few organisms escape from the lungs and mediastinal lymph nodes to form tiny foci of infection in other parts of the body. It may be manifest only by an unusual persistence of complement fixation or an elevated sedimentation rate. Even these signs may be inconclusive if the lesions are small enough. The extrapulmonary infection may be well combatted and eventually eliminated with subsequent regression of the complement fixation titer, or it may flare up several years after presumed recovery. Even a tiny focus in the wrong place—as in the meninges—may play havoc.

Dissemination sometimes seems to occur several years after the primary infection. Most of the evidence indicates, however, that late dissemination is more apparent than real. It is usually postulated only in retrospect, either from autopsy studies or from reconstruction of the case history after a tardy diagnosis. When cases are followed from the beginning of the primary infection, as was done in thousands of army cases, late dissemination is not observed. If the fungus is going to escape from the lungs and mediastinal nodes because of failure of immunologic defenses, it will do so in the first weeks or months. Dissemination rarely occurs in the second year. Late dissemination is but the emergence of an obvious lesion in the course of a previously inapparent dissemination. As Smith points out,[3] once the disease has become disseminated, the risk of continued dissemination is great even if remissions intervene because of the continuing vulnerability of the immunologically defective.

Sometimes trauma has been said to precede the appearance of a disseminated lesion. The unreliability of a history of antecedent trauma in other diseases is notorious. Trauma occurs so often in everyday life that any sort of lesion may call to mind a minor injury that may seem to be causally related. It may therefore be that the evidence of preceding trauma in coccidioidal infections is purely circumstantial. On the other hand it may be true that in the course of disseminated disease an injury sometimes causes localization of the fungus. An analogous situation has been noted in experimental infections with other fungi: animals given certain experimental mycoses may develop local lesions only where the skin has been shaved.

## ACUTE MILIARY DISSEMINATED COCCIDIOIDOMYCOSIS

There are two types of coccidioidal disease which may cause death shortly after the primary infection (1) acute meningitis discussed in the next section and (2) acute miliary disseminated coccidioidomycosis In my experience early miliary dissemination has occurred in about a fifth of the cases of generalized disease In a series of six cases of miliary dissemination I saw recently death occurred in from 25 to 110 days after the first symptoms This syndrome is most common in Negroes and Filipinos The third case of coccidioidal granuloma reported in North America (Ophuls first) was an example of acute miliary dissemination death occurring in about 90 days [11]

In this variety of infection seeding of the organism throughout the body must begin almost as soon as the lung is invaded Signs of distant metastases begin to appear in little longer than is required to grow the fungus in the test tube Primary and secondary phases cannot be distinguished Not many days after the first respiratory symptoms the body virtually explodes with metastatic lesions Death may occur even before the characteristic serologic titers of dissemination have had a chance to develop

An illustrative case history follows

A 35 year old Filipino farm laborer was perfectly well until eight days before admission to the hospital when he had sudden cough fever and stabbing left chest pain He lost 12 pounds of weight in a week At the time of entry he was a thin prostrated young man with a temperature of 103 F and a pulse rate of 140 There were signs of pulmonary consolidation over the upper half of the left chest Roentgenograms showed complete consolidation of the left upper lobe (Fig 27A) The leukocyte count was 17 500 per cu mm with 87 per cent neutrophiles The erythrocyte sedimentation rate was 30 mm per hr The coccidioidin skin test (1 100) was positive *Coccidioides* was cultured from the sputum and the blood The precipitin titer for coccidioidal infection was 4 plus at 1 40 and the complement fixation titer 2 plus at 1 8

Six days after admission verrucous skin lesions harboring *Coccidioides* appeared on the cheeks arms and legs A week later a roentgenogram showed miliary lesions in the right lung (Fig 27B) He died 25 days after the onset of the respiratory infection Post mortem examination showed innumerable coccidioidal lesions in the lungs skin subcutaneous tissue lymph nodes spleen and liver

When the course is somewhat longer than that described above the complement fixation titer becomes maximally elevated or shows such irregularities as the pre zoning phenomenon Roentgenograms may show destructive lesions of the bones Sometimes the skin of the face and other

parts of the body is a mass of confluent granulomas. Chills, high remittent fever, and profuse night sweats are characteristic. Blood cultures and bone marrow cultures are often positive for *Coccidioides*. Sputum may be profuse, purulent, and bloody. Occasionally the presenting symptoms are constipation, bloating, and abdominal pain simulating bowel obstruction. Sometimes lymphadenopathy suggests metastatic carcinoma or lymphoma. Rarely the urine contains protein and casts like those seen in glomerulonephritis. At autopsy the lungs are filled with large abscesses and extensive areas of necrosis interspersed with tiny miliary tubercles. Under the microscope there are masses of granulation tissue with epithelioid cells and multinucleated giant cells, as well as the birefringent endosporulating spherules of *Coccidioides immitis*. The bones, especially the ribs, may be destroyed by abscesses filled with thick, creamy pus. The pleural spaces may contain pale yellow fluid and the pleural surfaces may be studded with tubercles. Lesions varying in size from microscopic tubercles to large abscesses may be scattered profusely through the lymph nodes, liver, spleen, kidneys, adrenals, testes, muscles, joints, and skin.

Peculiarly enough, miliary dissemination often spares the central nervous system. Conversely, when fulminating meningitis follows hard upon primary coccidioidal pneumonia, gross lesions are often limited to the lungs and meninges, sparing other viscera. The two types of rapidly fatal coccidioidomycosis are therefore typically distinct.

## COCCIDIOIDAL MENINGITIS

Meningitis may be acute, subacute, or chronic. Although this type of coccidioidal disease is always fatal, the life span varies from a few weeks to more than ten years.

As mentioned previously, meningitis may appear during primary coccidioidal pneumonia and speedily kill. Except for the different pathologic findings, it is hardly distinguishable from acute miliary dissemination. It occurs most commonly in Filipinos and Negroes. Characteristically the patient has a severe attack of coccidioidal pneumonia from which he does not recover. Fever, lassitude, anorexia, and weight loss continue with no remission following the primary stage. Unless it is specifically sought, mild stiffness of the neck may be overlooked and the patient may waste away and die with the neurologic lesion undiagnosed. If the spinal fluid is examined, it is found to be yellow and turbid with cells. Sometimes it clots immediately because of the high protein content.

Unlike chronic meningitis, which typically causes only a low complement fixation titer, acute coccidioidal meningitis is accompanied by a high titer, often maximal. Skin sensitivity to coccidioidin, often strong in chronic meningitis, may fail in acute meningitis. This serologic pattern

may mean that the total mass of infected tissue is small in the chronic form because pulmonary involvement is now minimal whereas the total mass of infected tissue both pulmonary and nervous is large in the acute form

At autopsy not only the brain but also the lungs mediastinal lymph nodes and often the pleura are involved in the granulomatous process Other viscera are often spared

In Caucasian patients meningitis more often runs a subacute or chronic course It begins insidiously a month or two after the primary pulmonary infection which may be recalled only in retrospect as a vague respiratory illness Headache is usually the first symptom It often is a gradually increasing dull ache but sometimes it is sudden and severe Signs of meningeal irritation—a stiff neck and positive Kernig s sign—are observed The patient becomes forgetful confused and drowsy he may have convulsions or complain of double vision His gait is unsteady The pupils may be unequal and the disks choked Groups of muscles may be weak There is sometimes a low grade fever but often the whole course is afebrile Anorexia and vomiting may occur so that weight loss may be severe The face becomes thin expressionless and tragic The hands tremble and reflexes are over active The patient remembers how to feed himself and to care for his simple needs but little more He requires an hour or two to eat a small breakfast mumbling to himself between bites Though sometimes surly and whining he often remains pathetically pleasant like a faithful pet Gradually his simple comprehension dulls he loses sphincter control decubitus ulcers appear and he slips into a deepening coma to die of hypostatic pneumonia The disease runs its course in about four to twenty four months

There is a third form of the disease so indolent and so slowly progressive that long periods of apparently good health may intervene between the onset and the final decline with internal hydrocephalus Rare patients have lived for over ten years During symptomatic remissions only the spinal fluid may reveal that not all is well

In subacute or chronic coccidioidal meningitis abnormal laboratory findings are often limited to the spinal fluid The leukocyte count is usually normal although there may be a low grade eosinophilia The erythrocyte sedimentation rate may be normal or slightly elevated The coccidioidin skin test is typically positive The roentgenograms of the chest may be normal or may show the scars of the primary pneumonia Roentgenograms of the skull occasionally show bony defects or destruction of the sella or clinoid processes more often they are normal Ventriculograms though not ordinarily indicated may show symmetrical dilatation of the ventricular system Precipitin titers for coccidioidal infection

are often positive early in the disease indicating the recency of the primary infection The complement fixation titer is often so low that it is equivocal It may rise moderately to 1 16 or 1 32 as the disease progresses Spinal fluid may also fix complement usually in lower titer than the serum

The characteristic changes like those of tuberculous meningitis are found in the spinal fluid Its pressure is usually elevated sometimes to over 600 mm of water It is turbid and often yellow Its cells are increased often to 500 and sometimes to several thousand per cu mm Polymorphonuclear leukocytes predominate early and lymphocytes later Occasionally there are significant numbers of eosinophiles Protein is increased often to several hundred mg per hundred ml The colloidal gold curve is grossly abnormal the greatest elevation being in the first zone of the curve Sugar is characteristically decreased *Coccidioides* is not always easy to isolate from the spinal fluid but culture is positive often enough to make the procedure worthwhile If a test tube of spinal fluid is allowed to stand at room temperature for a month or so a cottony growth of *Coccidioides* often appears

In chronic coccidioidal meningitis pathologic changes are for the most part limited to the central nervous system The primary pulmonary lesion may not be detectable although granulomatous lesions may be found in the mediastinal lymph nodes The rest of the viscera are ordinarily spared although occasionally meningeal involvement is but a part of generalized chronic dissemination

Coccidioidal meningitis has been the most regularly fatal form of chronic disseminated coccidioidomycosis Experimental therapeutic agents which appear to have arrested other sorts of coccidioidal disease have not altered the course of meningitis Because it may be a slow remitting disease evaluation of drugs is difficult

## CHRONIC PROGRESSIVE DISSEMINATED COCCIDIOIDOMYCOSIS

Slowly progressive generalized coccidioidal infection is the commonest type of disseminated disease Its spectrum is wide and it shades imperceptibly into other forms of dissemination Classical coccidioidal granuloma is of this variety Posadas original case and Rixford's first case were the prototypes each patient lived for several years with relentlessly expanding lesions of the skin bones and viscera [1]

No single pattern is representative of the life history of this type of disease The primary phase of coccidioidal infections is not always recalled particularly by Caucasians Negroes and Filipinos are more likely to remember the more severe primary infections to which they are prone If the original illness has passed unnoticed the first symptom is usually

a skin eruption a swollen lymph node or a subcutaneous abscess The prognosis depends upon the number and sites of extra pulmonary metastases Skin and subcutaneous tissue are usually involved in one way or another Other common locations are lymph nodes bones joints spleen liver kidney and pleura Lesions of these various organs and systems are discussed separately in Chapter Eight

Chronic disseminated coccidioidomycosis may follow one of several courses (1) steady progression (2) long persistence without progression (3) remissions and exacerbations and (4) apparent cure

(1) *Steady Progression* There may be progressively greater involvement of skin bones and internal viscera until death Sometimes secondary bacterial infection of coccidioidal lesions is the lethal process Occasionally the destruction of a vital organ such as the adrenal cortex is incompatible with life

(2) *Long Persistence without Obvious Progression* Often a dynamic balance is achieved between invader and victim so that although metastatic lesions persist they do not spread significantly Parasite and host live together for years in a sort of symbiosis Sinuses continue to drain and the titer of complement fixing antibodies remains elevated but the general health of the patient otherwise remains good The truce is nevertheless precarious for it may be upset by anything which lowers the resistance of either combattant

(3) *Remissions and Exacerbations* Sometimes lesions spontaneously regress or disappear giving false hope of cure Persistence of a high titer of complement fixing antibodies and elevation of the sedimentation rate belie the apparently favorable course Fatal recurrences have followed years of presumed recovery

(4) *Apparent Cure* Now and then recovery appears to be real for disappearance of complement fixing antibodies parallels healing of the lesions In a few cases many years of good health have followed spontaneous regression of the obvious manifestations of the infection In the present state of our knowledge however so favorable a judgment in the individual case must be tentative

## ISOLATED PERIPHERAL GRANULOMA

Although this form is fundamentally no different from the type of chronic disseminated coccidioidomycosis described above its relatively good prognosis makes a separate discussion useful The name designates that type of chronic disseminated coccidioidomycosis in which there is only one obvious extra pulmonary lesion and that in a location which does not endanger life It has been known to persist for over thirty

years. Smith reported single extrapulmonary lesions in 75 (18 per cent) of 409 cases of dissemination.[illegible]

Lesions typical of this form are chronic granulomas of the hand and wrist or of the ankle and foot. Most often the peripheral disease begins insidiously without a recognized primary pulmonary lesion. The patient tells of a "boil" which will not heal. There are often several minor surgical procedures to incise and drain the abscess before bacteriologic studies reveal the diagnostic spherules. The lesion is characteristically centered in the bone—coccidioidal osteomyelitis. Sinuses undermine and perforate the skin variously about the limb. An ulcer heals only to have another appear sooner or later somewhere else. One of my patients suffered recurring sinuses, ulcers, and abscesses of the right wrist and hand for 20 years. Every year or two new lesions would appear, persist for several months, and then heal. There were no signs of the infection elsewhere and he appeared otherwise in robust health.

Dissemination of the disease from the peripheral lesion is thought by Smith not to occur,[85] but inasmuch as the lesion is itself evidence of an originally defective immunity response, there is always the danger that dissemination from the lung has already involved other sites.

If the lesion is extensive, the complement fixation titer may be high despite apparent general good health. This form of the disease may be a greater hazard to economic and social standing than it is to life. Because of the location, exacerbations are usually incapacitating.

The isolated peripheral granuloma is the most amenable to cure of all forms of chronic dissemination. Amputation of the involved extremity is often successful, although granulomas occasionally recur in the stump if the procedure is not radical enough. Some of the newer chemotherapeutic agents also offer promise in this type of coccidioidal disease. An illustrative case history follows.

For 11 years a 48-year-old Filipino man had an ugly coccidioidal granuloma of the left hand and wrist.[1] Several minor surgical procedures were done over a period of 9 years before the diagnosis was established. Carpal and metacarpal bones were distorted and fused into a hapless conglomerate. The fingers and hand were useless. Skin and subcutaneous tissues were a foul, suppurating mass swimming with spherules of *Coccidioides*. Surgical intervention seemed advisable, but because the patient refused amputation, ethyl vanillate was tried. Within six days the skin began to heal. Sinuses closed one by one, although organisms were not immediately eradicated from their depths. A few months later the hand and wrist were covered by soft, supple skin. Sinuses had disappeared. Useful motion was returning to the fingers. The complement fixation titer had fallen from 1:256 to 1:64. He was thereafter well for several years before a minor exacerbation occurred.

*Chapter Thirteen*

# Coccidioidal Disease in Lower Animals

The possibility of coccidioidal disease in animals was suggested in the earliest papers concerning the first human victim Wernicke concluded his historic study of 1892 by promising to report the results of animal inoculation experiments then in progress[3] Posadas kept his mentor's promise by publishing descriptions of the disease produced by the parasite in monkeys and other animals[1]

When Rixford and Gilchrist described the first North American case they also recounted a series of animal experiments the significance of which was even greater than they realized[8] Unable yet to grow the fungus on culture media they inoculated the skin of dogs and rabbits with debris from the lesions of their patient Two rabbits died of pyogenic infections but in their bodies no parasites could be found In three other rabbits and two dogs only self limited cutaneous coccidioidal lesions could be produced All these animals recovered completely and could not there after be successfully inoculated with the organism Obviously they all had primary coccidioidal infections which healed without dissemination but the significance of the experiment could not have been appreciated until the discoveries of Gifford and Dickson forty years later

When Ophuls[14, ‥] proved *Coccidioides* to be a fungus not a protozoan he did so in part by serial passage through animals He found that intraperitoneal inoculation of guinea pigs produced progressive granulomatous lesions of the abdominal viscera and testes but that subcutaneous inoculation produced only local lesions When a pure culture of the fungus was injected into an ear vein of a rabbit the animal developed lesions in the lungs spleen and kidneys—demonstrating hematogenous dissemination Cold blooded animals—i e frogs—remained healthy even after inoculation into the peritoneal cavity

The first instance of naturally occurring coccidioidomycosis in animals was reported in 1918 by Giltner[r] who described *Coccidioides* in the bronchial and mediastinal lymph nodes of cattle slaughtered in an

abattoir in San Diego. In experiments pursuant to his discovery, he successfully inoculated guinea pigs, rabbits, dogs, cattle, sheep and swine, noting that their susceptibility to coccidioidal infections decreased in about the order named. Hypodermic inoculation of calves produced only a brief localized infection of the skin and subcutaneous tissues, whereas severe and rapidly fatal pulmonary disease followed intravenous injection. Sheep he found were more resistant, for subcutaneous inoculation produced almost no detectable lesions, and intravenous injection caused a chronic generalized infection which was fatal only after eight months. The pig was most resistant of all. Even intravenous injection caused at most only minimal asymptomatic nodules in the lungs, liver, and at the inoculation site.

Beck[101] first described naturally acquired coccidioidal lesions in sheep. Her survey for the California State Department of Public Health[133,134] soon thereafter revealed that the bronchial and mediastinal lymph nodes of many cattle from Southern California contained *Coccidioides*, and in the next few years there were reports of similar findings in other southwestern states.

It was early noticed that coccidioidal disease in cattle is not symptomatic. Lesions were at first seen only in mediastinal or bronchial lymph nodes. In 1937, about the time that primary human coccidioidomycosis was being described, Davis, Stiles, and McGregor also reported granulomatous lesions in bovine lungs. They assumed that the disease began in the thoracic lymph nodes and spread to the lungs. In retrospect their observations are perfectly clear. They thought that the pulmonary lesions represented dissemination, but it is now obvious that they represented the original lesions, antedating even those in the lymph nodes. Subsequent studies have demonstrated that, as in man, *Coccidioides* enters the lung through inhalation.

In a study of 511 animals found to have coccidioidal lesions of the lung and lymph nodes in Phoenix, Prchal noted that all of them had been fattened for 2 or 3 months in dusty feedlots which often contained 6 to 12 inches of manure, dust, and debris.[4] He did not find the disease in animals brought in directly from the range. Most of the affected animals were Hereford steers. Pre-mortem examinations never gave evidence of symptoms, and lesions were never extensive enough to warrant condemnation of the carcass. The only economic importance of the infection has been the necessity of differentiating its lesions from those of tuberculosis.

According to Maddy, 59 per cent of the horses and many burros in the Phoenix area have positive coccidioidin skin tests.[8] Lesions have been noted only rarely in sheep, but the infection may be more common

among them than is recognized at present Only one instance of infection in swine has been noted [9]

In 1940 Farness first described spontaneously acquired coccidioidomycosis in a dog a Great Dane with widespread dissemination [3] Numerous other reports of canine coccidioidomycosis have been made one of the most comprehensive being a discussion of 52 cases by Reed of Tucson [9,3] His review suggests a variation in breed susceptibility to dissemination analagous to the variation among human races Twenty six (50 per cent) of his cases concerned Boxers the other 26 were spread among 11 other breeds

Most of the reports of canine coccidioidomycosis have until recently dealt only with disseminated lesions According to Maddy who has studied several hundred cases the dog is the only important animal which displays disseminated lesions similar to those of man [9] The canine disease is similar to the human except that osseous lesions tend to be proliferative rather than lytic

Several recent papers have demonstrated a benign non progressive form of coccidioidal infection in dogs Levan and Burger described a primary pulmonary coccidioidal disease analagous to the Valley Fever of human beings [8,13] An 18 month old female Scotty had weakness anorexia fever and cough Roentgenograms showed a pulmonary infiltrate *Coccidioides* was isolated from the sputum and the complement fixation test for coccidioidal disease was positive Although she recovered completely a kennel mate with a similar primary pulmonary disease died not long afterwards of fulminating disseminated coccidioidomycosis In a series of autopsies on 34 stray dogs in Tucson only one of whom appeared to be ill Straub and Schwarz found coccidioidal lesions in the lungs and hilar lymph nodes of eight [9,9]

Ajello and his co workers recounted an epizootic among 5 Collie dogs in Tucson [8,9] The spectrum of symptoms was as broad as that seen in man One dog had an acutely fatal infection two died after long wasting illnesses one survived a lengthy illness and one recovered rapidly from a brief febrile episode It was found that the animals sniffed rodent burrows from which *Coccidioides* was later isolated The habit of investigating rodent holes shown by Egeberg and Ely to be likely sites of contamination [9] may in part explain canine susceptibility to coccidioidal infections

In 1942 Emmons reported coccidioidal lesions in the lungs and lymph nodes of rodents native to southwestern deserts [3] He found that autopsy studies of deer mice *(Peromyscus)* pocket mice *(Perognathus)* kangaroo rats *(Dipodomys)* and ground squirrels *(Citellus)* provided data for nicely delimiting endemic areas He once proposed that the rodents form the

reservoir of infection[31] but now feels that they like man and domestic animals are but accidental hosts

Artificially induced coccidioidomycosis of primates was first described by Posadas who noted that among animals the monkey is particularly susceptible to the infection dying in twenty to thirty days after inoculation[15] Spontaneously occurring primate infections in the San Diego Zoo were reported by McKenney Traum and Bonestell[36] In 1936 microscopic examination of the lungs of a tropical American monkey showed spherules of *Coccidioides* Several years later a rapidly fatal infection occurred in a mountain gorilla a 15 year old animal who suffered anorexia weight loss fever dyspnea and nasal hemorrhage Lesions were present in the liver spleen lungs and lymph nodes

In 1953 Jasper reported coccidioidal disease in a chinchilla[4] The infection has also been noted in a llama in California[97] *Coccidioides* was reportedly found in a Townsend mole in Seattle Washington but the identification was almost certainly in error[499] Feline species have so far not shown susceptibility to coccidioidal infection The house cat is conspicuously absent from lists of coccidioidomycosis in lower animals

Infection in animals is usually considered to be due to inhalation of contaminated dust Cronkite and Lack by the use of a device with which mycelial spores could be transmitted to the guinea pig s nostril without contaminating the rest of the body closely mimicked natural conditions and produced typical primary pulmonary coccidioidomycosis On the other hand Rosenthal[r] reported in 1950 that if guinea pigs with experimental pulmonary infections were housed with normal guinea pigs the latter sometimes developed spontaneous infections However although he described positive coccidioidin skin tests pathologic changes in the lungs and spherules in direct mounts of the lesions the published photographs of the spherules contain no endospores and in no case was the fungus recovered by culture Smith has never observed such changes although he has repeatedly housed healthy animals with infected

Levan and Burger[7] have postulated that dogs are sometimes infected by contact with one another but Ajello s epizootic studies cited above suggest the alternative explanation of a common source of dust borne spores

Lubarsky and Plunkett studied the susceptibility of non mammalian animals to experimental coccidioidal infection[819] In crayfish goldfish and certain reptiles arthrospore containing nodules could be produced but typical infections with development of spherules did not follow intra abdominal injections of mycelial suspensions In the rock lizard however widespread lesions resembling those in mammals appeared to be produced

In summary only mammals with rare exceptions have heretofore shown susceptibility to coccidioidal infection In general the pattern of infection is similar to that in man i e the naturally occurring disease may be a self limited pulmonary infection but in certain species it may become widely disseminated to the abdominal viscera bones subcutaneous tissues and central nervous system Primates and dogs appear susceptible to both primary and disseminated infections with variations of susceptibility among races or breeds Rodents cattle horses burros and to a less extent sheep and swine are susceptible to benign primary pulmonary infections Certain species such as the cat are not known to be susceptible

Spontaneous infections occur in cattle burros horses llamas swine sheep dogs ground squirrels rabbits rats and mice of the desert monkeys gorillas chinchillas and probably also in other animals not yet reported Guinea pigs white mice and other animals are also susceptible to experimental infections The spontaneous disease like that in man is usually due to the inhalation of dust borne spores

*Chapter Fourteen*

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# Treatment of Coccidioidomycosis



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## PROPHYLAXIS AGAINST COCCIDIOIDAL INFECTION

THE BEST treatment of coccidioidal disease would be its prevention. Prophylaxis could conceivably be accomplished in two ways: (1) preventing contact between the fungus and the susceptible and (2) artificially inducing immunity in the potential host. The first prospect would involve the impossible task of eliminating either the susceptible or the fungus from endemic areas. It is obvious that susceptibles will not remain away, for the endemic areas are almost synonymous with the areas of most rapid population growth in the United States. Even members of the most highly susceptible races will not avoid the danger zones in view of the demand for agricultural laborers. It is even more unlikely that the fungus will be eliminated from the vast reaches of its desert habitat. This aim can be approximated on a small local scale by dust control measures as Smith and his colleagues demonstrated so clearly in the air fields of the San Joaquin Valley during World War II,[4] an approach which is highly proper for protecting the short term resident in an endemic area but which would only postpone the infection of the permanent inhabitant.

The most promising way of preventing infection would seem to be the production of artificial immunity in susceptibles, i.e., vaccination. Pre-

liminary studies are already under way Vogel Fetter Conant and Lowe using a vaccine of heat killed spherule suspension demonstrated increased resistance of guinea pigs to respiratory challenge by *Coccidioides* [8,7] Friedman and Smith using killed mycelial spores showed increased resistance of mice to intraperitoneal challenge [10,11] Ninety five to 100 per cent of the vaccinated mice survived for 60 days compared to only 20 per cent of the controls Perhaps the most promising field of research concerning coccidioidal disease will be that of induced immunity If the peoples of the southwestern United States—particularly those of the susceptible races and those newly arrived for agricultural labor—could be effectively vaccinated against *Coccidioides* the problem of coccidioidomycosis would be essentially solved

## TREATMENT OF PRIMARY COCCIDIOIDOMYCOSIS

Only the minority of cases of primary coccidioidomycosis require consideration of treatment Most cases are asymptomatic and leave only a positive skin test and permanent immunity as sequelae Patients with mild symptoms instinctively modify their activities even without benefit of medical care just as they would for any other respiratory infection Inasmuch as they will almost certainly speedily recover no matter what is done or not done it is probably just as well that their disease remains undiagnosed in view of the widespread apprehension among the laity concerning Valley Fever Unfortunately such undue apprehension is too often also felt by the physician so that he prescribes restrictions that would be considered ridiculous in any other mild respiratory disease I know of a child who was kept in bed nearly a year after a mild attack of coccidioidal erythema nodosum Since he had only one chance in several hundred of suffering dissemination and since there is no evidence that excessively prolonged rest would avoid the hazard in the ill fated case anyway the child was unnecessarily robbed of a year of his life The almost invariable benignity not the rare hazard should be stressed to most patients

The purposes of treatment of symptomatic primary coccidioidomycosis are (1) avoidance of dissemination (2) restoration of the patient to normal activity and health as soon as possible and (3) reassurance of the patient that his chances of future trouble are remote and that complete recovery and permanent immunity are to be expected Inasmuch as we are uncertain about all of the factors that predispose to dissemination the first purpose stated above is as yet theoretic—an ideal rather than a *fait accompli*

The preliminary step in planning treatment is an evaluation of the hazard of dissemination If the patient is a member of one of the dark

skinned races so prone to dissemination, then strict precautions are demanded. If he is Caucasian, restrictions may be minimal.

There is as yet no specific therapy for primary coccidioidomycosis, so that the physician has only two measures in his armamentarium: (1) symptomatic treatment and (2) restriction of activity. Aspirin and codeine are used as necessary to relieve pleuritic pain, headache, myalgia, backache and arthralgia. The diet is limited only by the appetite. Bed rest is prescribed until the acute symptoms subside. In severe infections this will mean absolute bed rest. White patients may be allowed out of bed when fever and signs of pneumonia have subsided. Activity should still be limited for two or three weeks after the acute stage, until the sedimentation rate is back to normal, the roentgenologic lesions are clear or static and the serologic titers are low or falling. The patient should not return to heavy activity for a month after the sedimentation rate has returned to normal and other signs are negative. Premature physical exertion often causes exacerbation of symptoms and elevation of the sedimentation rate.

Occasionally the roentgenogram does not clear completely. Fibrosis may be stubborn or permanent, and nodular lesions may remain. The patient may be considered to have recovered satisfactorily when the roentgenographic lesion has stabilized and other signs of active infection have regressed.

The complement fixation titer sometimes persists at a low level for months in otherwise healthy people. If the titer is falling and if the sedimentation rate is normal, recovery is considered adequate.

To be perfectly frank, it is hard to develop evidence that the eventual course of the disease is much altered even by the restriction of activities prescribed above, although by analogy to other diseases it would seem to be the course of discretion. Winn strongly feels that strict rest is in order until the process is "focalized," for it is in this period that the die is cast, the only time when the physician has even a theoretic control of the eventual outcome.[96] On the other hand, many physicians have taken a much more relaxed attitude without evidence of adverse reactions. Dr. Peter Meis of Davis Monthan Air Force Base in Arizona recalls that during the Korean "police action," when demand for flight personnel was pressing, he returned officers and men to duty while they still had residual pulmonary infiltrations, reasoning that "their lungs will heal as readily in an airplane over Korea as in a bed in Arizona."[99] The outcome, at least in those cases, seemed to vindicate his judgment.

***The Use of Antibiotics and Steroids.*** Should antibiotics be given during acute coccidioidomycosis? When the diagnosis is apparent, this question may not arise, for *Coccidioides* is uninhibited by clinically attainable levels of penicillin, streptomycin, chloramphenicol, tetracycline and its de-

rivatives or any other commonly used antibiotic[364, 3 0, 393, 418, 5 7, 899] Their use is likely to be considered for two reasons (1) when a respiratory infection is not recognized as coccidioidal and (2) when secondary bacterial infection is suspected or its possibility is feared The first reason requires no comment but the second deserves honest appraisal

Only occasionally will massive secondary infection of a pulmonary lesion require antibiotics In large series there are but a few cases of bacterial invasion of acute coccidioidal cavities and the production of pyogenic abscesses If antibiotics in coccidioidomycosis were entirely harmless the question would be academic only But it is a practical problem both economically and medically Several weeks administration of antibiotics at the necessary current prices presents a financial problem to many patients

There are two objections from the medical standpoint In the first place there is the general hazard of a reaction to antibiotic drugs—skin eruptions fever blood changes diarrhea and even anaphylactic deaths Secondly there is a theoretic hazard—slight to be sure—that some antibiotics may even make a coccidioidal infection worse Keeney and his associates have shown that certain concentrations of penicillin stimulate *Coccidioides immitis* in vitro[334] Precise clinical data are lacking but dissemination is occasionally seen in white patients who have been treated for long periods with antibiotic drugs The rarity of this catastrophe in Caucasians makes a controlled series all but impossible

On the other hand certain clinicians feel that bronchiectasis is more common in areas of coccidioidal endemicity than elsewhere It has therefore been proposed that the transient bronchitis of primary coccidioidomycosis should be treated with nebulized antibiotics to reduce secondary invasion of traumatized bronchial mucosa[613]

Cortisone and ACTH are generally considered to be contraindicated in primary coccidioidomycosis because of their possible interference with the immunity mechanisms of the body Newcomer and others have shown that cortisone has a slightly adverse effect on the survival of animals with experimental coccidioidal infections[784] The rapid development of permanent immunity is the outcome most heartily to be desired Any therapy that may imperil the body s resistence is suspect no matter how much it may alleviate symptoms temporarily

Nevertheless it must be admitted that the contraindication to steroid therapy in primary coccidioidomycosis is mainly theoretical Levan and Einstein have reported a number of cases in which cortisone was used unwittingly for coccidioidal erythema nodosum and in which no apparent harm was done[914]

***Treatment of Erythema Nodosum and Multiforme*** Inasmuch as the specific erythemas are themselves the signs *par excellence* of a usually good prognosis treatment is simply relief of symptoms and congratulation of the patient on his happy prospects Unless the lesions are unusually painful or tender nothing is required but aspirin or perhaps codeine The antihistaminics have been used by some and local applications of soothing and astringent lotions or packs by others Cortisone rapidly controls erythema nodosum but as mentioned above its safety in coccidioidal disease is as yet uncertain In a few cases unusually severe erythema nodosum has been treated with steroids without untoward results Otherwise treatment is as described above for the respiratory illness

***Treatment of Primary Coccidioidomycosis in the Members of Susceptible Races*** Because the resistance of Negroes and Filipinos to progressive coccidioidomycosis is so notoriously poor in their case much of *what has been said above must be modified* Overstressing the importance of the disease is the danger to Caucasians but the Negro and Filipino may take it too lightly As soon as the diagnosis is suspected dark skinned patients should be placed at bed rest which should continue for a month or so after the acute stage even in the absence of symptoms It is true that rest has not been proved to fend off dissemination but in the absence of evidence one way or the other caution would seem to be the only defensible course Often enough the infection progresses despite absolute bed rest

Whenever specific drug therapy becomes available the Negro or Filipino patient with a severe primary infection will be the first candidate for its use There is already a little evidence that dissemination can be aborted in its incipient stage by the early use of coccidioidocidal drugs [31] *One may predict that when there is finally a safe effective and easily ad*ministered drug for treatment of disseminated coccidioidomycosis it will also be given routinely to Negro and Filipino patients during the primary *phase At the present time there is no agent which fills these criteria al*though in the individual case the use of one of the experimental drugs may even now be warranted

## TREATMENT OF CHRONIC BENIGN RESIDUAL PULMONARY LESIONS

As discussed in Chapter Eleven solid pulmonary lesions or coccidioidomas do not require treatment per se but because *there is no way of* absolutely ruling out a malignant lesion without biopsy (which in this situation requires thoracotomy) surgical resection is almost always indicated *even though the patient's health* is not thereby improved Coccidioidomas may also require surgical intervention if they are expanding

Cotton, whose experience with resectional surgery for coccidioidomycosis has been large, once stated that his indications for surgical intervention were giant cavity, secondary infection, rupture (with spontaneous pneumothorax, empyema, or bronchopleural fistula), non-expansile lung, and continued or severe hemoptysis.[41] More recently he has favored removal of *all* chronic cavities, symptomatic or not, because of his experience that even with good medical care complications are only postponed and that surgery will eventually be necessary.[849] Forsee, whose published series is second in size only to Cotton's, has also stated his opinion that cavities are best treated by surgical removal, even in the absence of distressing symptoms.[79] It is perhaps significant that some of the advocates of the more radical approach live outside of the endemic area and are therefore more likely to see only the cases in which symptoms are severe.

Various surgical procedures have been successfully used to eradicate cavities. Occasionally, even a local "shelling out" of a cavity suffices.[53] More often, wedge resection, segmental resection, or lobectomy are done.[79, 849] Decortication is performed when the pleura is involved, as in an empyema or bronchopleural fistula, although sometimes repeated thoracenteses suffice for empyema. In the days before antibiotics were available thoracic procedures were often followed by serious complications, but in recent years such hazards have been reduced to a minimum. Cotton has reported that even in the presence of active coccidioidal empyema, decortication may be followed by prompt re-expansion of the lung and healing by first intention.[849]

Cavities sometimes recur after otherwise successful surgery, usually in the over-expanded parenchyma of the same lung. I know of a case in which cavitation recurred after each of two surgical procedures separated by more than a year. Krapin and Lovelock,[41] Hyde,[801] Forsee and Perkins,[87] and Cotton, Paulsen and Birsner[849] have also reported this complication. On the whole it is of infrequent occurrence.

## TREATMENT OF DISSEMINATED COCCIDIOIDOMYCOSIS

Treatment of disseminated coccidioidomycosis is a subject to be approached with humility. We do not yet have the answer, although research continues apace in several interesting directions.

It is a sobering experience to study and report with cautious optimism a new therapeutic agent for coccidioidal disease, as I have done, only then to read an ancient article with almost the same words and results concerning a drug now long discredited. One has but to see the old accounts of occasional "cures" with antimony and potassium tartrate, sodium iodide, colloidal copper, or a dozen others, "cures" as dramatic as any we can re-

late now to realize the vagaries of coccidioidal infection The course of the untreated disease is so unpredictable and erratic that evaluation of any drug is exceedingly difficult Only a large series perhaps larger than that which one man will see even in endemic areas will be necessary to give the final answer In the meantime we must continue to try the most promising agents must look at our results honestly and a little incredulously and must not take ourselves too seriously

An honest appraisal of 60 years of various forms of treatment compels these observations

(1) The course of acute fulminating disseminated coccidioidomycosis has never been altered by any form of therapy past or present

(2) Meningitis has also probably not been affected by treatment at least not often enough to draw any conclusions

(3) Dramatic improvement of chronic disseminated lesions has coincided with *treatment* by several methods and with *many drugs* *It has* also occurred with no treatment whatsoever

(4) Drugs which have apparently been curative in some cases have failed in other similar cases

(5) Apparent eradication of disseminated lesions may be followed ten or fifteen years later by severe or fatal recurrence

These disquieting observations must temper any discussion of treatment of disseminated coccidioidomycosis Incredulous realism though perhaps not complete therapeutic nihilism is in order

## Chemotherapy of Disseminated Coccidioidomycosis

A problem arises when the results of in vitro studies with chemotherapeutic agents are applied to clinical work for it is often uncertain whether the pharmacologic characteristics of *Coccidioides* are the same in the saprophytic and parasitic phases Perhaps the fungus in its two phases acts like two different organisms It may be that the concentration of a drug which is lethal to the mycelial form in the test tube is quite different from that which kills the spherule form in living tissues Methods which perpetuate spherule propagation in vitro may therefore be required in order to test the effectiveness of drugs

The list of agents which have been discarded never generally accepted or not yet adequately tried is a long one (Table VII) Some of the experimental drugs which are currently under consideration are described below

***Prodigiosin*** Prodigiosin a purple tripyrrole methane derived from cultures of *Serratia marcessans (Bacillus prodigiosus)* inhibits *Coccidioides immitis* in vitro and is effective against experimental coccidioidal infection

in animals.[535] Wier, Egeberg, Lack and Leiby reported its use in 14 cases of disseminated coccidioidomycosis, in several of which it was thought to be life saving.[771] Egeberg later concluded that the initial favorable impression had been based in part on a misconception of the natural history of the disease in Negroes.[193] Although prodigiosin may be of value when applied locally, opinion has not supported its use in generalized disseminations.

TABLE VII

SOME OF THE AGENTS PROPOSED FOR TREATMENT OF COCCIDIOIDOMYCOSIS WHICH HAVE BEEN DISCARDED OR INADEQUATELY TESTED

Methyl violet
Tincture of iodine
Potassium bromide
Oil of turpentine
Carbolic acid
Potassium permanganate
Colloidal copper
Gold salts
Colloidal lead
Thymol
Potassium iodide
Creosote
Guaiacol
Antimony and potassium tartrate
Roentgen therapy
Gentian violet
Bismuth
Typhoid vaccine
Coccidioidin
Copper sulfate
Lead acetate
Mercury cyanide
Novasurol
Bismuth potassium tartrate
Iodobismitol
Sodium thiosulfate
Fundin
Sulfonamides
Convalescent serum
Penicillin
Streptomycin
Streptothrycin
Salicil
Plumbagin
Bacillomycin
Chloraquin
Histamine
Chloromycetin
Protoanemonin
Fradicin
Thiolutin
Rimocidin
Candicidin
Para amino benzoic acid
Hydroxychloraquin

***Cycloheximide.*** Cycloheximide (Actidione®), a substance derived from cultures of *Streptomyces griseus*, inhibits a number of fungi in vitro. It has been reported upon favorably in several cases of progressive coccidioidomycosis. Some of the reports concerned chronic coccidioidal meningitis, in which the course may be long and variable even without treatment.[601] Cohen and Gifford reported the case of a boy with widespread abscesses and osseous lesions who was treated with cycloheximide for a year.[133] When he died of a sympathicoblastoma several years later, no *Coccidioides* organisms were recovered by culture.

Perhaps the most devastating commentary on the value of cycloheximide is the fact that it is used in the selective medium of Georg, Ajello and Gordon because it allows *Coccidioides* to grow while inhibiting other fungi.[1613]

***Stilbene Derivatives.*** Stilbamidine, 2-hydroxystilbamidine and aminostilbamidine have been tried in the treatment of disseminated coccidioidomycosis following their successful use in cases of histoplasmosis, blastomycosis and sporotrichosis. Several papers report apparently good results

occasion oral administration has coincided with clinical improvement in disseminated coccidioidomycosis but it has not happened often enough to know whether the relationship was causal or merely due to chance[869] Administered intramuscularly, the drug has proved to be too toxic causing chills fever malaise and local pain and tenderness Several intravenous preparations at first showing promise, have been disappointing because of thrombophlebitis and febrile reactions even with small doses

*Amphotericin B* Amphotericin A and B are antifungal agents derived from an unidentified species of *Streptomyces* obtained from soil on the banks of the Orinoco River in Venezuela[911] Amphotericin B is similar in its antibiotic spectrum to nystatin but it is absorbed slightly more readily from the intestine It has been shown to possess an inhibitory if not curative effect against *Coccidioides* in experiments in the mouse Clinical experience has been inconstant At times it has appeared effective both when given by mouth and by vein An immediate and striking—but temporary—remission was wrought in one of my cases[918] In some other cases there has been no observable effect[911] It appears that the fungus may acquire resistance to the antibiotic

*Sex Hormones* Both androgens and estrogens have been used experimentally in coccidioidomycosis Stilbestrol[8] and testosterone[910] compounds inhibit the fungus in vitro Cohen reported that diethylstilbestrol seemed to be helpful in one of his cases[910] but Piper[81] reported two treatment failures with it Lamb[911] described one case of disseminated coccidioidomycosis in which improvement accompanied administration of testosterone (100 mg per day) and triple sulfonamides (1 Gm three times daily) In another instance improvement of coccidioidal synovitis coincided with administration of a combination of estrogen androgen and trypsin[911]

*Isonicotinic Acid Hydrazide* Isonicotinic acid hydrazide has been shown to have no effect in experimental coccidioidal disease[774] Its use has been reported in several primary and one disseminated infection[884] As would be expected even if untreated those patients with primary coccidioidomycosis did well Whether the improvement in the case of dissemination was related to the therapy only further study will show

*Other Agents* Among the medications which Cohen has tried are sodium caprylate[81] which he considers to be useful as a topical application the sodium salt of cinnamic acid[813] oil of sassafras[813] which he uses in both primary and secondary coccidioidomycosis because of its ease of administration[81] and 5 nitro-2 furfuryl-3-chlorpropionate

Maddy has tried "Captan" a fungicide used in agriculture in the treatment of disseminated coccidioidomycosis in dogs In several cases

there was striking improvement Preliminary trials in human coccidioidomycosis as yet unpublished are promising

### Surgical Treatment of Disseminated Coccidioidomycosis

Although surgical intervention has most often been used for benign residual pulmonary lesions it is occasionally successful in disseminated coccidioidomycosis particularly in isolated peripheral granulomas Inasmuch as there is no assurance that the visible peripheral lesion is the only site of dissemination such surgery is not always helpful but in certain cases it is worth considering Lesions confined to limbs have often been eradicated by excision or amputation but other alternatives should be considered before undertaking radical surgery If the lesion is limited to one part there is a chance that one of the more promising medical agents may salvage the limb If the disease is not limited to one limb amputation will probably not alter the final outcome in any case Nevertheless amputation may occasionally still be indicated for an extensive deforming granuloma that has rendered an extremity unsightly and worse than useless

Other surgical procedures are sometimes worthwhile Cautery of peripheral lesions has been advocated [164] most recently by Winn [96] Sometimes excision of a fungating granuloma of the trunk or extremities while not curing the disease will eliminate its most objectionable evidence and return the patient to reasonably normal social status Curettment of osseous abscesses may be followed by new bone formation Diseased joints are occasionally much improved by synovectomy [8 3 5] Removal of female adnexa has abolished coccidioidal pelvic inflammatory disease in several cases[388] although other disseminated lesions may later be fatal [63 844] Nephrectomy for renal coccidioidomycosis has apparently restored good health [844] Removal of the diseased testes or epididymis is also often successful [630 3 871] Excision of sinuses down to and including their origin in abdominal viscera arrested the disease in one of my patients

Unfortunately the outcome is not always so favorable even when the process is local for the scar or stump may sooner or later be involved in a lesion as extensive as that for which the operation was done [8] In general surgery is likely to remove not the disease but only its evidence but at times it may be well worth while

### General Measures in Treatment of Disseminated Coccidioidomycosis

In the absence of more conclusively effective specific therapy general hygienic and supportive care is still an important part of treatment Rest is advised in proportion to the severity of the disease although it is hard to determine just how harmful physical activity actually is In fulminating

dissemination and coccidioidal meningitis there is no choice the patient is bedridden till death The question most often arises in cases of isolated peripheral granuloma during a stage of relative quiesence It is probably not harmful to allow a little activity or even light work if the patient feels capable of it Certainly it is good for his morale Patients often tolerate heavy work even when the physician warns against it but exacerbations sometimes follow overly strenuous exertion Perhaps they would have occurred anyway

## CONCLUSION

Most of the subjects discussed in previous chapters have the authority of complete and accurate scientific data In general our knowledge about coccidioidomycosis is sure Our understanding of its medical therapy is on the other hand faltering and uncertain This situation is not unique We are often faced with the paradox of intimate acquaintance with a disease and embarrassing confusion about its cure Etiologic knowledge and pathologic understanding usually precede therapeutic skill Much was known about diabetes before insulin was available the hemolytic streptococcus and the havoc it works were clearly discerned before penicillin was discovered Therapy is often the last frontier

It will be thus with fungus *Coccidioides* The meager therapeutic results already achieved at least demonstrate that coccidioidomycosis is not necessarily incurable Because coccidioidal disease has heretofore been mainly of regional interest research concerning its therapy has not always had high priority Were it as ubiquitous as lobar pneumonia or poliomyelitis the answer would already be at hand With the expanding population of the southwestern states and the increasing interest in fungus diseases throughout the nation research concerning coccidioidal disease will be intensified and a definitive means of therapy will sooner or later be found

*and coccidioidomycosis published from 1892 to July 1954 with a subject index by Charles R Nicewonger, M A distributed in mimeograph form by the School of Public Health University of California My bibliography includes all of Nicewongers titles except for a dozen which were for various reasons excluded as well as some two hundred others A few titles in the Index Medicus and Current List were also excluded it being apparent that their listing under Coccidioidomycosis" was incorrect*

It is inevitable that there will be errors both of omission and inclusion in such a list as this but it is submitted as a usable working basis for further investigation


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